UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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NEUROLOGICAL DEVICES PANEL

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February 10, 2012
8:00 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, Maryland

PANEL MEMBERS:

ROBERT W. HURST, M.D.	Chair
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RICHARD G. FESSLER, M.D., Ph.D.	Non-Voting Member
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LYNDA J. YANG, M.D., Ph.D.	Non-Voting Member
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ANNE W. ALEXANDROV, Ph.D.	Consumer Representative
DAVID H. MUELLER, M.S.	Industry Representative
LT AVENA RUSSELL, ABD, M.S.	Designated Federal Officer

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Solace Medical, LLC

COL KATHY PLATONI, Pys.D.

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Neuronetics

BRANDEL FRANCE de BRAVO
National Research Center for Women and Families

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M E E T I N G

(8:00 a.m.)

DR. HURST: I would like to call this meeting of the Neurological Devices Panel to order.

I'm Dr. Robert Hurst, the Chairperson of this Panel. I'm an interventional neuroradiologist and vascular neurologist at the Hospital of the University of Pennsylvania.

I note for the record that the voting members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the Panel participating in the meeting today has received training in FDA device law and regulations.

For today's agenda, the Panel will discuss and make recommendations regarding the possible reclassification of cranial electrotherapy stimulator, or CES, devices. In 2011, FDA issued a proposed rule which, if made final, would make CES devices Class III, requiring premarket approval. In response to the proposed rule, FDA received petitions requesting a change in classification. The Panel's discussion will include the existing data to support CES safety and effectiveness and whether the data is sufficient to develop special controls to support regulation of these devices under Class II.

Before we begin, I would like to ask our distinguished Panel members and FDA staff seated at this table, beginning on my left, to

introduce themselves. Please state your name, your area of expertise, your position, and affiliation.

DR. EYDELMAN: Good morning. My name is Malvina Eydelman. I'm Director of the Division of Ophthalmic, Neurological and ENT Devices at the FDA.

DR. STEIN: I'm Murray Stein. I'm a psychiatrist at the University of California, San Diego, and I work in the area of anxiety and stress disorders.

DR. ARRIA: Good morning. My name is Amelia Arria, and I'm a psychiatric and addiction epidemiologist. I work both at the University of Maryland and at the Treatment Research Institute in Philadelphia.

DR. YANG: Good morning. I'm Lynda Yang. I'm a neurosurgeon from the University of Michigan.

DR. GOOD: Good morning. My name is David Good. I'm Professor and Chair of Neurology at Penn State/Hershey Medical Center, and my major interests are stroke and recovery from stroke.

DR. DORSEY: Good morning. My name is Ray Dorsey. I'm a neurologist at Johns Hopkins and specialize in movement disorders such as Parkinson's disease.

DR. KOTAGAL: Good morning. My name is Suresh Kotagal, and I'm a pediatric neurologist and a sleep specialist at Mayo Clinic in Rochester, Minnesota.

LT RUSSELL: Good morning. My name is Avena Russell, and I'm the Designated Federal Officer for the Neurological Devices Panel.

DR. ANDERSON: Good morning. My name is Karen Anderson. I'm a neuropsychiatrist at the University of Maryland. I'm at the movement disorders group. My interests include Parkinson's disease, Huntington's disease, and deep brain stimulation surgery.

DR. STEIER: Good morning. My name is Kenneth J. Steier, D.O. I'm the Clinical Dean at the Touro University College of Osteopathic Medicine in New York City, and I'm a pulmonary and critical care physician.

DR. EVANS: Good morning. Scott Evans, Senior Research Scientist, Biostatistics, Harvard University.

DR. FESSLER: Good morning. My name is Richard Fessler. I'm a neurosurgeon at Northwestern University.

MS. CARRAS: Hi, I'm Michelle Carras. I'm the Patient Representative, and I'm a first-year Ph.D. student in the Johns Hopkins Bloomberg School of Public Health.

DR. ALEXANDROV: Good morning. I'm Anne Alexandrov. I'm Assistant Dean and professor at the University of Alabama, Birmingham School of Nursing, and I'm a Consumer Rep.

MR. MUELLER: Good morning. My name is David Mueller, and I'm in regulatory affairs for American Medical Systems, and I am the Industry Representative.

DR. HURST: If you have not already done so, please sign the attendance sheets that are on the tables by the doors.

Lieutenant Avena Russell, the Designated Federal Officer for the Neurological Devices Panel, will make some introductory remarks.

LT RUSSELL: Good morning. I will now read the Conflict of Interest and Deputization to Temporary Voting Member Statements.

The Food and Drug Administration is convening today's meeting of the Neurological Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the Industry Representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S. Code Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this Panel are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S. Code Section 208, Congress has authorized FDA to grant waivers to special Government employees who have financial conflicts when

it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest. Under Section 712 of the Food, Drug and Cosmetic Act, Congress has authorized FDA to grant waivers to special Government employees and regular Government employees with potential financial conflicts when necessary to afford the Committee essential expertise.

Related to the discussion of today's meeting, members and consultants of this Panel who are special Government employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for the purpose of 18 U.S. Code Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, the Panel will discuss and make recommendations regarding the possible reclassification of cranial electrotherapy stimulator devices (CES). The Panel discussion will include the existing data to support CES safety and effectiveness and whether the data are sufficient to develop special controls to support regulation of these devices under Class II. This is a particular matters meeting during which special matters related to CES devices will be discussed.

Based on the agenda for today's meeting and all financial

interests reported by the Panel members and consultants, a conflict of interest waiver has been issued in accordance with 18 U.S. Code Section 208(b)(3) to Alvaro Pascual-Leone, M.D. However, he was unable to attend this meeting.

David Mueller is serving as the Industry Representative, acting on behalf of all related industry, and is employed by Mueller and Associates.

We would like to remind members and consultants that if the discussion involves any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participant needs to exclude themselves for such involvement and their exclusion will be noted for the record. FDA encourages all other participants to advise the Panel of any financial relationships that they may have with any firms at issue. A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

I will now read the appointment of temporary voting member status.

Dr. Amelia Arria, Dr. Murray Stein, and Michelle Carras have been appointed to serve as a temporary non-voting member of the Neurological Devices Panel for the duration of the meeting on February 10th, 2012.

For the record, Dr. Arria serves as a consultant for the

Anesthetic and Analgesic Drug Product Advisory Committee at the Center for Drug Evaluation and Research (CDER).

Dr. Stein serves as a member of the Psychopharmacologic Drug Advisory Committee at CDER.

Ms. Carras serves as a consultant and Patient Representative for the Psychopharmacologic Drug Advisory Committee at CDER.

These special Government employees have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting.

This appointment was authorized by Jill Hartzler Warner, J.D., Acting Associate Commissioner for Special Medical Programs, on February 9th, 2012.

Before I turn the meeting back over to Dr. Hurst, I would like to make a few general announcements.

Transcripts of today's meeting will be available from Free State Court Reporting and company. The telephone number is (410) 974-0947. Information on purchasing videos of today's meeting can be found at the FDA meeting registration desk.

The press contact for today's meeting is Michelle Bolek.

I would like to remind everyone that members of the public and the press are not permitted in the Panel area, which is the area beyond the speaker's podium. I request that reporters please wait to speak to FDA

officials until after the Panel has concluded.

If you are presenting in the Open Public Hearing today and have not previously provided an electronic copy of your slide presentation to FDA, please arrange to do so to Ms. Ann Marie Williams at the registration desk.

In order to help the transcriber to identify who is speaking, please be sure to identify yourself each and every time as you approach the podium to speak.

Finally, please silence your cell phones and any other electronic devices at this time. Thank you very much.

Dr. Hurst.

DR. HURST: We'll now proceed to the reclassification overview by Ms. Marjorie Shulman, Acting Director, Premarket Notification (510(k)) Program.

I would like to remind public observers that while the meeting is open for public observation, public attendees may not participate except at the specific request of the Panel Chair.

Ms. Shulman.

MS. SHULMAN: Thank you. Good morning. Again, my name is Marjorie Shulman, and I'm Acting Director of the Premarket Notification 510(k) Program, and this morning we're going to discuss device reclassification.

So, what is the purpose of the meeting today? It's to provide input to the Food and Drug Administration on whether sufficient scientific evidence exists to develop appropriate special controls to reclassify a pre-amendments device from Class III to Class II.

So, what is a pre-amendments device? It's a device type that was introduced into interstate commerce prior to May 28th, 1976, which was the enactment of the Medical Device Amendments.

So, how are pre-amendments devices classified? Originally, back in the late '70s, early '80s, they received a recommendation from a device classification panel, published the panel's recommendation for comment, along with the proposed rule classifying the device, and then published a final rule classifying the device.

Each of the known pre-amendments devices that are out on the market prior to May 26th, 1976 were classified into I, II, or III. The ones that were classified into Class III, Class III is premarket approval, PMA, and until the FDA could call for PMAs or reclassify the devices, they're reviewed as Class III 510(k)s.

So, what are the device classes? They're classified based on the controls necessary, and a device should be placed in the lowest class whose level of control provides reasonable assurance of safety and effectiveness. So, there's classes, Class I, which is general controls; Class II, general and special controls; and Class III, premarket approval.

So, Class I devices are for devices which general controls by themselves are sufficient to provide reasonable assurance of the safety and effectiveness of the device. And most Class I devices are exempt from 510(k) or premarket notification prior to being marketed.

The general controls include such things as prohibition against adulterated or misbranded devices, good manufacturing practices, registration of the manufacturing facility, listing what devices are made there, recordkeeping, repair, replacement, and refund, et cetera.

These are some examples of Class I devices: adhesive bandages, manual stethoscope, patient scales, exam lights, and crutches.

Class II is for devices that cannot be classified into Class I because the general controls by themselves, the Class I general controls that I just covered, are insufficient to provide reasonable assurance of the safety and effectiveness of such a device, and for which there is sufficient information to establish special controls to provide the assurance. Class II devices typically require premarket notification or 510(k) prior to being marketed, although some Class II devices are exempt from 510(k).

Special controls include such things as performance standards, postmarket surveillance, patient registries, development and dissemination of guidance documents, et cetera.

So, some examples of Class II devices are ventilators, ECG machines, endoscopes, hemodialysis system, sutures, syringes, powered

wheelchairs, and CT machines.

Special controls are used. So, for example, surgical sutures are Class II devices. FDA has issued a special controls guidance document to mitigate the risk to health, and in this guidance document it requires biocompatibility testing; sterility testing; conformance to the USP monograph; reabsorption profile testing for absorbable sutures; of course, labeling, which we have specified warnings, precautions, adverse reactions, et cetera. So, these special controls, in combination with the general controls, the Class I's, could provide reasonable assurance of safety and effectiveness. So, applicants must provide evidence in their 510(k) how the special controls were addressed.

Class III devices are Class III because they cannot be classified into either I or II because insufficient information exists to determine that the general or the general and special controls are sufficient to provide the reasonable assurance of safety and effectiveness; and the devices are life sustaining and/or life supporting, or of a substantial importance in preventing impairment of human health, or present a potential or unreasonable risk of illness or injury. Class III devices require premarket approval, also known as PMA, prior to being marketed.

Some examples of Class III devices: implantable pacemakers, implantable spinal cord stimulators, IUDs, and extended wear contact lenses.

So, pre-amendments devices where FDA has issued a proposed

rule classifying them into Class III; however, no final rule was issued. So, that's what we have today; they're pre-amendments Class III devices and no final rule was issued. Then a final rule did issue to publish it in the Code of Federal Regulations, but the rule did not contain a date by which companies are required to submit a premarket approval application. So, therefore, these Class III devices were allowed and are allowed to proceed to market by the 510(k) process, until such a time either we call for PMAs, premarket approval, or a reclassification is finalized.

So, the process. What we do is the FDA can reclassify a pre-amendments device in a proceeding that parallels the initial classification proceeding, the ones that took place in the late '70s, early '80s, based upon new information respecting the device, either on FDA's own initiative or upon the petition of an interested person, and the Agency classifies or reclassifies the device for the intended uses which have actually been reviewed by the Agency.

After this Panel meeting, the FDA will consider the available evidence, including the input of the Panel. We will issue a final rule classifying the device either into Class II or III. If Class II, existing devices would be subject to any identified special controls and may continue to market. And if Class III, existing devices will remain on the market but must submit a PMA by a specified time frame. And then if that premarket approval application is not received and filed, they would have to be removed from the

market.

Thank you.

DR. HURST: We'll now hear from Mr. Timothy Marjenin, team leader for the Division of Ophthalmic, Neurological and Ear, Nose and Throat Devices, on the CES devices regulatory history.

Mr. Marjenin.

MR. MARJENIN: Good morning, distinguished Panel members, members of industry and audience members. My name is Tim Marjenin and I'm the team leader for the proposed rule. I'm a biomedical engineer and reviewer in the Division of Ophthalmic, Neurological and Ear, Nose and Throat Devices in ODE. And over the next few slides I'm just going to give you an idea of the rationale for the meeting, a brief device description, and a regulatory history for CES devices.

FDA issued a proposed rule on August 8th, 2011, to require premarket approval for cranial electrotherapy stimulation devices, which are most commonly known as CES. The proposed rule included a public comment period, which closed on November 7th, 2011, and interested members of the public were invited to submit information to the docket, and many submissions were received. The proposed rule also provided an opportunity for interested parties to request a change in classification through a petition to the Agency.

Subsequent to the publication of the rule, FDA received three

petitions to request a change in classification for CES devices. FDA is required to seek panel input on the information in the petitions, and we are therefore asking for your expertise and input at an open public meeting of the Neurological Devices Panel.

Though they're Class III, as Ms. Shulman just mentioned, CES devices are currently reviewed through the 510(k) pathway and are allowed onto the market if their indications for use and technological characteristics are determined to be substantially equivalent to a legally marketed predicate device.

The earliest CES devices relied on a comparison to the pre-amendments devices in order to demonstrate substantial equivalence. And as you just heard, pre-amendments devices were on the market prior to May of 1976, when the Medical Device Amendments were enacted. Over time, this has given way to the use of predicate devices that FDA has evaluated and found to be substantially equivalent, but you can still trace these back to the pre-amendments devices.

There are 15 total submissions for CES devices that FDA has found to be substantially equivalent. The first one was cleared back in 1977.

CES devices are defined by the regulation, which states that they are devices that apply electrical stimulation, electrical current, to a patient's head to treat insomnia, depression, or anxiety.

And, technologically, CES devices really only consist of two

main components. The first is the enclosure that houses the stimulation electronics, and the second consists of the cutaneous electrodes.

Older CES devices tended to be larger stationary devices, and newer CES devices tend to be small enough to be handheld, such that they can be worn by patients while moving around, though this is not always the case. And the devices shown on this slide are among the 15 that have been found to be substantially equivalent.

It is also important to briefly highlight what is not considered CES. Electroconvulsive therapy, or ECT, is also a pre-amendments Class III device, and it also treats psychiatric disorders by applying the current directly to the head. However, it is applied at levels that, per its regulation, induce a major motor seizure. CES output is much lower in comparison.

Transcranial magnetic stimulation, or TMS, is used to treat depression as well. However, TMS devices function by inducing a current through an electromagnetic coil placed on the patient's head. This is a different technology. TMS devices are Class II. They are post-amendments devices.

Transcutaneous electrical nerve stimulation devices, or TENS devices, are intended for pain relief. Many have a higher output than CES, allow for greater control of the stimulation parameters, and generally include warnings against electrode placement that allows current to flow through the head.

These are simply examples of device types that are regulated separately from CES, though they may appear similar in their intended use or technology. Throughout our presentation later this afternoon, FDA will not use any of the device types highlighted on this slide as a basis for comparison to CES because they are regulated separately.

And on the following few slides I'll present an overview of the regulatory history. Additional details can be found in FDA's Executive Summary.

As I stated previously, all CES devices that were on the market prior to May 1976 are considered pre-amendments, in reference to the Medical Device Amendments.

CES was discussed at two classification meetings. The first one took place in 1977. The results of the discussions and presentations were a split classification. The first part was for situational anxiety resulting from detoxification from drugs or alcohol, which was recommended for Class II by a four to three vote. The second, treatment of sleep disorders, was recommended Class III by unanimous vote.

The minutes from the meeting note that there was also a unanimous vote to advise FDA that the reason for the split vote regarding the Class II use was a difference of opinion among the panel members about the device's efficacy.

CES was discussed at a second classification meeting in

January 1978. This panel returned to the discussion of the split classification, and concerns were raised about the data that had been presented previously. This panel revised the recommendations of the first panel. The transcript states that "the meager consensus today holds that these devices be considered for both applications, namely, tension and anxiety, and for sleep induction, and that they be placed in Class III."

The proposed and final rules for the classification of CES were published in 1978 and 1979, respectively. The final rule defined the CES regulation as a device that applies electrical current to a patient's head to treat insomnia, depression, or anxiety. The classification rule listed the Class III recommendation because satisfactory effectiveness has not been demonstrated.

These rules also included several other statements, based on the panel proceedings, as justification for the Class III recommendation. They noted that it was not possible to establish an adequate performance standard for CES because the characteristics needed for effective stimulation were not known.

The rules also noted that CES presents potentially unreasonable risk of illness or injury to the patient if the practitioner relied on the device and the device proved to be ineffective in treating the illness.

In 1993 FDA issued a proposed rule, similar to the one published in August of 2011, that would require premarket approval for CES

devices. The 1993 proposed rule reiterated concerns from the classification rule, such as the lack of knowledge about the stimulation characteristics that are necessary for effectiveness.

The proposed rule also noted that there had been no systematic study identified in the literature that attempted to determine the characteristics that are necessary for effectiveness. Listed first among the risks was a worsening of the condition being treated due to the device not being effective.

FDA received two reclassification petitions after this proposed rule was published, but both were closed without panel input because they were incomplete, and the petitioners did not respond to requests for additional information.

FDA also received several comments in response to this proposed rule, citing issues relating to valid scientific studies and behavioral science as well as the risks associated with the use of the CES device. All of these comments were reviewed and addressed in the final rule, which was published in 1995 and required the submission of PMAs rather than 510(k)s for CES devices.

However, in January 1997, FDA issued a proposed rule to revoke the PMA requirement for CES devices. The rule noted that FDA had since become aware of additional information relevant to the possible reclassification of the CES device.

It also stated that it was necessary to revoke the final rule from 1995 while pursuing possible reclassification, so that the existing CES devices could remain in commercial distribution. This rule was proposed in January of that year and was made final that June.

At the same time that the final rule revoking the PMA requirement was issued, FDA also published a 515(i) notice requesting CES manufacturers to submit information about the safety and effectiveness of the devices. A 515(i) is only a request for information, though it may later lead to rulemaking. Submissions were received from two manufacturers, but no further actions were taken at the time.

In 2009 FDA issued a 515(i) notice for all of the remaining Class III pre-amendments devices, in order to begin final rulemaking for all of them. CES remained part of this group as a result of the revocation of the 1995 final rule. Therefore, manufacturers were required to once again submit safety and effectiveness information for CES devices.

FDA received submissions from four CES manufacturers as well as a manufacturer not required to submit because they have no device currently on the market. Each one was reviewed to determine whether the devices should be down-classified to Class II or if premarket approval should be required.

FDA also performed a literature search for CES studies published after the 1993 proposed rule, which included studies through

mid-2010. FDA excluded many of the studies from further review because they were conducted on very specific populations that were not representative of the general population suffering from insomnia, anxiety, or depression. FDA identified several studies, as well as two meta-analyses, for further review.

Based on the review of the 515(i) submissions received from CES manufacturers and the literature review, FDA concluded that the effectiveness of CES has not been established by adequate scientific evidence, and the Agency continues to agree with the panel's recommendation.

FDA concluded, therefore, that a premarket approval requirement was warranted, and a proposed rule outlining the concerns was published in August 2011. In the rule, FDA reiterated the concerns of the original classification panels as well as those identified in the 1993 proposed rule. Also included was a discussion of the information that had been reviewed. This included the 515(i) submissions and the literature search.

As noted previously, there was an opportunity for interested parties to request a change in classification, and FDA received three such petitions. In addition to reviewing each petition, FDA also conducted a new systematic literature review, which will be presented later.

As noted, FDA received three petitions. One of the petitions has requested a change in classification for the indications that are stated in

the regulation and have been used for cleared CES devices, namely, to treat insomnia, depression, or anxiety.

The other two petitions have proposed indications for use that includes treatment of depression, anxiety, and insomnia in adult substance abuse patients who have failed to achieve satisfactory improvement from one prior antidepressant or sleep medication at or above the minimal effective dose and duration in the current episode, or are unable to tolerate such medication. Both indications are proposed for prescription use only.

FDA received approximately 200 comments regarding the 2011 proposed rule. Because the petitions are the focus of this Panel meeting, this slide and the next are intended to provide only an overview of the docket. All of the comments will be fully addressed as part of the final rule.

Comments were submitted by a wide variety of individuals. Roughly half came from patients who have used CES and their family members. A large number of comments were also submitted by healthcare practitioners, including but not limited to psychiatrists, psychologists, physical therapists, acupuncturists, dentists, social workers, and one veterinarian. There were also several submissions from employees of CES manufacturers and CES distributors.

A few of the comments from patients agreed with FDA's proposed classification. But overall, if a comment expressed an opinion about the classification of CES devices, it was in favor of the Class II

designation. These opinions were generally based on firsthand experience either as a healthcare practitioner or a patient, and sometimes both. Although the comments report on the effectiveness of CES for a range of conditions and note a general lack of serious adverse events, the evidence is largely anecdotal in nature. FDA did ensure that any literature references that were submitted were checked against the list that was generated as part of the new systematic review.

Of the comments that were received, many identified one or more indications for use. The predominant use, as mentioned, included anxiety, depression, and insomnia, between 85 to 120 mentions for each. Specific disorders were not generally cited, although there were several comments that specifically mentioned conditions such as obsessive compulsive disorder or post-traumatic stress disorder. Substance-related treatment uses were mentioned in approximately 20 comments.

Pain is called out here only because it was mentioned in approximately 90 comments in one form or another. Use for other conditions, such as pain, that are unrelated to anxiety, depression, and insomnia, such as ADHD, migraine, or macular degeneration, were mentioned no more than a few times each. Pediatric uses were mentioned in approximately 10 comments.

Please note that only the indications listed in the petitions are under discussion today.

Thank you.

DR. HURST: Thank you. We will now proceed with the Open Public Hearing portion of the meeting.

Public attendees are given an opportunity to address the Panel to present data, information, or views relevant to the meeting agenda. Lieutenant Russell will now read the Open Public Hearing disclosure process statement.

LT RUSSELL: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with any group or company that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any financial relationships. If you choose not to address this information of financial relationships at the beginning of your statement, it will not preclude you from speaking.

DR. HURST: There's been a request to speak by the following, beginning with Rhys Thomas, Solace Medical, LLC; Colonel Kathy Platoni, private practitioner; Douglas Harding, FutraMed, Incorporated; Dr. Brian Earthman, practitioner; Dr. Paul Rosch, the American Institute of Stress; Dr. Diana Zuckerman, National Research Center for Women and Families.

Each speaker will be given approximately five minutes to address the Panel. Please be sure and state your name, company, and any affiliation with the petitioners as you are asked also to approach the podium.

And we'll begin with Rhys Thomas, Solace Medical.

MR. THOMAS: Thank you. I'm Rhys Thomas. I'm with Solace Medical, and I am a distributor of Alpha-Stim devices, just so that you all know where I stand.

You'll have to forgive me because I'm actually having a side effect from a drug, and that's caffeine, right now. A little bit of jitteriness, but no big deal.

I'm going to give you a little bit of background as to what I've done in the past. I used to work in the pharmaceutical industry, and I was a pharmaceutical rep. I also did hospital representative office space, I did manage care and long-term care and hospice. So, I have a lot of experience within the pharmaceutical industry from 1985 to 2004. At that time I got laid off, and you all know what's been going on in the pharmaceutical industry.

Anyway, I worked a lot with pain medications. Pain management was one of the big issues that I had covered because of the medications of the company that I represented had. But I also have a lot of experience in the field with anxiolytics, antidepressants, and sleep medications, especially in relation to those other -- to the pain medications.

And, obviously, from a pharmaceutical industry standpoint, one of the things that you're going to discuss a lot with people is the side effect profiles of these medications. And in my experience in working with the pharmaceutical industry, the side effects were really pretty significant, and you can see that in package inserts with almost everything.

If anybody's interested, I brought some information from a couple of different companies that market anxiolytics, antidepressants, and sleep medications, and they have package inserts in them. So, you all probably have seen them already, but I do have some information there, a lot of information on side effects, also interactions. There have been abuse and diversion of a lot of these medications, as you all know. The costs are pretty significant, both to the public, as far as their pocketbook goes, and to society as a whole.

Actually usually one or two --

DR. HURST: Excuse me. Thank you, Mr. Thomas. However, your time is up.

MR. THOMAS: Wow, five minutes went fast.

DR. HURST: Take a couple seconds there to just finish up, but --

MR. THOMAS: Okay.

DR. HURST: -- we are going to try to hold pretty strictly to the five minutes.

MR. THOMAS: Okay, I'm sorry.

Yeah, the effect on the cranial electrotherapy stimulation side, what I've seen in the offices in comparison was that we've been able to actually see results with patients in the office setting, and side effects haven't been an issue. But if there's more time a little later, I'll be glad to come back up.

Thank you. Sorry.

DR. HURST: Thank you, Mr. Thomas.

Next will be Colonel Kathy Platoni, private practitioner.

DR. PLATONI: Good morning, distinguished Panel members. My name is Dr. Kathy Platoni. I am a clinical psychologist, a colonel in the United States Army Reserve, and I am the Army Reserve psychology consultant, which you loosely translate to chief psychologist for the Army Reserve. However, I am here today as a civilian practitioner with substantial human experience in both the civilian sector and in the wartime theaters of both Iraq and Afghanistan. It is my belief that we must absolutely maintain the right to use CES for our private patients, our service members, and our veterans.

My disclosure is that I have no financial or equity interest in any CES company, nor am I a consultant for any CES company. I have not been compensated to be here today. However, my travel expenses only have been paid.

I have extensive experience utilizing CES since 1991 in hospital-based pain management programs, private practice and, again, the wartime theaters of both Iraq and Afghanistan. Although I am not a researcher, in my role as both a civilian practitioner and as an Army psychologist, I am required to thoroughly evaluate each patient to determine diagnosis, proper course of treatment, and to assess treatment results on a continuous basis.

Currently, approximately 95% of my private practice patients are in possession of their own personal Alpha-Stim devices. This was a difficult process because of the current classification. I sincerely hope that this process can be simplified if CES is moved to Class II.

In my experience, without exception, there simply is no more powerful form of therapeutic intervention, either as an adjunct or as a standalone treatment, than Alpha-Stim CES. It is incumbent upon me as a practitioner to offer all of those treatment interventions that may affect positive outcomes, all inclusive, hence CES.

In the wartime theaters of both Iraq and Afghanistan, and under the worst possible conditions that any human being should ever be forced to tolerate, Alpha-Stim CES was the single most effective form of

treatment that our combat stress control team was able to provide to service members in our care.

In terms of insomnia, CES was the best form of treatment we had to get soldiers to sleep where sleep is elusive. The use of CES spread to other practitioners once they viewed such positive results.

In terms of anxiety, nothing worked better to treat anxiety than CES, and again under the most stressful conditions imaginable. In the face of desperately depressed soldiers consumed with overwhelming misery and despair, the rapid and progressive effects of CES made it possible for these soldiers not only to perform their missions but actually to exceed standards and expectations. And with respect to PTSD, most importantly, soldiers were able to remain on mission.

To deny access to CES will result in tremendous and unnecessary suffering among infinite numbers of patients who prefer not to shuffle through life stuporously as a result of medication side effects.

For all intents and purposes, for those who can no longer survive or subsist under prescriptive conditions, there too often is no perceivable course of action remaining other than the taking of their own lives, when boluses of multiple medications fail to reduce or ameliorate any number of psychological injuries and conditions.

And what about saving lives? The deleterious impact of the FDA's decision threatening access to CES in the USA is immeasurable and will

unquestionably potentiate an endless series of damages to those so urgently in need of Alpha-Stim CES.

So, my question to you is what justification does the FDA have to burden a small business with requiring them to go through the process, the onerous process of premarket approval, when the same FDA allowed these devices to be legally marketed for 31 years, during which time there have been no significant side effects and an abundance of proof of effectiveness?

I will be here for the entirety of the day, and I'm available for questions. Thank you very much for your time.

DR. HURST: Thank you, Colonel Platoni.

Next will be Mr. Douglas Harding from FutraMed.

MR. HARDING: Distinguished Panel, it's a pleasure for me to be here, and I appreciate participating in this very important meeting. I'm Douglas Harding. I'm the President and Chief Technical Officer of FutraMed. I have a couple of my associates here as well. And FutraMed is in Utah, and we're a new company, though, in the CES market, as far as the fact that we don't have a product we're distributing yet. However, we are working on entering a new one here soon and thought our perspective may be worthwhile as a new company trying to enter this. We do have extensive experience in CES and other medical devices.

As you can kind of tell from the color of what hair I have left, I've been around for a while. I've been involved in a lot of these things, and

we do have a device that's ready. We've had collaboration with some of the CES pioneers in Europe, which have been helping us in our approach, and we've been working with them in developing that.

The CES obviously has technology well before the 1976 period, and there have been a number of CES devices marketed. And I thought it was kind of interesting. In 1974 the FDA panel did make a comment that significant side effects or complications attributed to the procedure are virtually nonexistent. And that's really what we found with the folks that we've worked with.

Now, FDA has mentioned a few side effects or a few risks, and I know that even from their literature they provided, that they showed a few of the adverse effects that have been noted. Many of those were from a long time ago, and really, I would hope the manufacturers have corrected those. I mean like from 1974, they pointed one out where it had a burn. I know that, at our company, we've been through all of those risks and hazards and have mitigated all of them. I looked at the MDR records for JXK product code and only saw three, and I think of those, none of those were any of the ones that were a big concern.

So, the risks have been mitigated. We've mitigated them ourselves. I believe that actually the safety record that you can see from what CES devices would indicate, that the risks have been mitigated, and it's not -- you know, we're not having the same things that the FDA is bringing up

from years a long time ago. But if you look at current things, there's very little problem from that.

And the benefits are amazing, and that's the reason I'm here, personally. I'm very passionate about what we're doing, and I see people that need it. I appreciated the presentation previous to mine. There is such a great need, and I think it's no question that there is a benefit and there's something that's there. And I think that even though we may not totally understand everything about it, we know it works, and people are being helped from it, and I think that's the reason I want to be involved.

Just to mention the PMA, I don't think it'll really help a lot to change things. I think you'll come up with the same results. And the other thing is a PMA will effectively stop a lot of research by small companies like myself, individuals that have a real passion, and you'll basically put people out of business and you'll be -- then you're going to be left with research from companies that I don't think are nearly as passionate as some of us.

But, anyway, I have some recommendations. First of all, I'd like to recommend that these are a Class II device. I think that definitely would be reasonable based on the safety of the devices over the years, the number of units that have been made and the few adverse situations and the potential benefit to the population of the United States.

I do think there should be some special controls. Some of the obvious ones with manuals, with using licensed people to do it, so it's not just

someone just doing it in their basement. And I think it'll also provide evidence to the FDA of the safety testing through FDA and IEC testing standards.

And I think one of the most important things that can help to satisfy the issue of safety risk and information is the thing that's so prevalent in our work now as quality companies, is the risk management system and plan. That goes along with the FDA requirements and ISO 14971. The risk management should include your product design, product utilization, post-surveillance. You look at all of the different hazards. You come up and you mitigate those. You determine risk from those hazards. You mitigate them. You provide that information to the FDA. To me, I think that's a marvelous way to handle it, much simpler and much more as effective as any PMA would do.

So, I appreciate the opportunity to present briefly to you. I wish I had a lot more time because I'm very passionate about this, and I think this is a wonderful technology, and I'm excited being involved in it.

DR. HURST: Thank you, Mr. Harding.

Next is Dr. Brian Earthman.

DR. EARTHMAN: I am Dr. Brian Earthman. I am a psychiatrist. I'm also the medical director for Electromedical Products International. I'm also a major in the United States Army Reserve. I am not representing the Army Reserve today; I'm representing myself, so the comments are from me.

Thank you for the forum. We do appreciate the time to talk about this. I wish I had as much time to talk with you about it as I do with my patients, but it's not what we have today.

First off, some of the specifics that are in the information. One question is the different patient populations and whether or not some of the research can be looked at because it's identified as being a separate patient population. Depression, anxiety, and insomnia are what's listed on the FDA language. These are not psychiatric diseases. These are symptoms. And to single out some of the research because it addresses a substance abuse population and the treatment of anxiety within that population is unfair in my opinion.

Another concern is the potential risks and the identified ones, including the worsening of the condition being treated as a result of ineffective treatment. I use it concurrently with medication. In fact, that's one of my big concerns with medication, is that when medication is started, that I'm going to make the condition worse because of the treatment. So, I think with any type of treatment, that's a concern. I have not experienced CES to make the conditions of my patients worse or to delay effective treatment.

There's also a question of potential adverse effects from electrical stimulation of the brain. At this point I don't see any evidence of this. And, again, you have to weigh the benefit versus the risk, and we have

to treat these disorders. And potential risk of seizure, I have not seen any of that. Skin irritation. I can't imagine skin irritation as being a barrier to treatment of depression or anxiety or insomnia, and what I have experienced with my patients has been minimal. Blurred vision I have not seen in my patients, and my understanding is that some of the blurred vision side effects had to do with some of the electrode placements in the past, and currently the Alpha-Stim CES uses electrodes on the ears. Okay.

Okay, as a practicing clinical psychiatrist, and 90% of my time is spent doing that, I need tools to treat my patients. The recent practice guidelines from the APA, the American Psychiatric Association, for treatment of depression, gave us information that shows that at 12 weeks, people who had initiated medication treatment had stopped their medication and they had not remitted. And basically what we know now is that we need more tools.

Okay, CES is one of those tools that's effective for me in my practice. Okay, at this point I've treated over 300 patients with CES, both in my outpatient practice, also in a theater of war in Iraq, and it's been extremely effective. I feel much more comfortable treating patients with CES, from a safety standpoint, than with medication.

The point was brought up earlier about treatment of insomnia in the theater. That's one of the great benefits for this treatment, is that a CES treatment will not leave you sedated and overmedicated. You actually

feel more relaxed and alert after a treatment. So, you don't have to worry about those potential side effects that come along with a lot of the insomnia medications.

That's basically what I want to let you guys know. As a treating psychiatrist, I need this tool to treat my patients. I'm not seeing negative benefits -- or negative side effects that would limit me from using this, and I sincerely hope that you guys will take an unbiased approach to the reclassification process for this device.

Thank you.

DR. HURST: Thanks, Dr. Earthman.

Next will be Dr. Paul Rosch.

DR. ROSCH: I'm President of the American Institute of Stress, and Clinical Professor of Medicine and Psychiatry at New York Medical College.

To save time I'll skip my background, training, certification, appointments, and awards and simply state that I've been involved in cranial electrotherapy stimulation research for over 25 years. We have regularly presented panels on this at our annual international congress in Switzerland, from the leading experts in the United States, Europe, and Russia.

I am an emeritus member of the Bioelectromagnetics Society and senior editor of *Bioelectromagnetic Medicine*, described in some reviews as the bible in the field. It has 17 chapters devoted to various aspects of

electrical brain stimulation, electromagnetic stimulation, by pioneers in the field, and also chapters devoted to mechanisms of action. And I call your attention to the one by -- coauthored with Dr. Bjorn Nordenstrom, who's formerly chairman of the Department of Radiology at Karolinska and chairman of the committee that selects the Nobel laureate in medicine.

My involvement is with the -- originally with the low-energy emission therapy device known as Symtonic. The Symtonic is a walkman-type device which has a coaxial cable and radiofrequency administered to an electrode that's applied to the roof of the mouth near the junction of the hard and soft palate where it's close to the hypothalamus. The Symtonic has been found to be effective in insomnia at two leading sleep laboratories in the United States. Changing the frequencies also allows it to be effective for the treatment of anxiety, as shown in a Harvard study, published in peer review journals, including the *New England Journal of Medicine.*

More recently, it's been found that altering these frequencies allows the delivery of electromagnetic current in the same way. It is the most effective treatment found for cancer of the liver. We've found that altering these frequencies allows you to target specific cancer cells, breast, prostate, both in patients and in cell culture studies.

I should mention that the amount of radiation delivered to tissues is 100 to 1,000 times less than that by a cell phone held to the ear.

The problem is that -- oh, I should also indicate that the FDA

recently approved Novocure, which is 24/7 CES for the treatment of malignant brain tumors. And pilot studies suggest that it's also effective for cancer of the lung and cancer of the pancreas.

Now, I want to emphasize that this shows a two-minute spectrum of EEG frequency versus amplitude, and you see in the upper left-hand side the profile in a normal pain-free patient. To the right a patient with pain due to degenerative joint disease. Down below you see the profile with the Liss device now currently marketed by Fisher Wallace and Alpha-Stim. You can see the Alpha-Stim more closely resembles a normal pain-free subject. That does not entitle you to say that it is superior. The point of that, and additional studies that also highlight the differences between these two devices, is that you cannot use the results of another CES device to support your claims of efficacy and safety. CES devices are not created equal, and they have to be evaluated on the basis of scientific studies preferably published in peer review journals.

Andy Bassett made this prediction in 1992. Bassett, along with Bob Becker, was one of the pioneers who --

DR. HURST: Excuse me, Dr. Rosch, you have about 30 seconds left.

DR. ROSCH: I'll just go right through that, about the medical device approval process, which is holding up progress, CDRH criticism by both commissioners, Congress, and more recently, the Institute of Medicine, and

what the recommendations are, the biggest problem being lack of transparency, lack of transparency about the selection of panel members, their qualifications, how they vote --

DR. HURST: Thank you, Dr. Rosch, but I think your time is up.

DR. ROSCH: All right. Thanks.

DR. HURST: Next will be Dr. Diana Zuckerman. Dr. Zuckerman?

(No response.)

DR. HURST: We've had one additional request to speak by Kevin Daggett.

MR. DAGGETT: Hello, my name is Kevin Daggett. I'm a registered addiction specialist and an auricular acupuncture specialist. I'm not compensated by any company, but my travel expenses have been arranged and paid for.

I don't feel I'm here speaking on behalf of any company in particular. I'm here speaking on behalf of people who suffer from addiction. I work in a treatment facility, and one of the biggest problems I see in the addiction field is how do you reduce recidivism rates and relapse rates?

And, first of all, you have to look at what are the causes of that, and from interviewing patients, some of the biggest causes are anxiety, depression, sleep disturbances, and chronic pain. A lot of the folks we see come in our facility suffer from chronic pain, get on pain medications for legitimate reasons, and then get addicted to it. How do they get off of it?

I started doing some research last year into -- see, I've got a little bit of experience in the past with some CES and how is it used in the addiction field and what's the success rate of it?

During that process I saw some good results online, some good information, and found about this reclassification hearing, and it seriously concerns me. We get a lot folks and put them on antidepressants to deal with their depression and anxiety. A lot of that stuff is addictive. Benzodiazepine, Xanax, Ativan, Valium, things like that can be addictive in their own rights and abused by folks.

I didn't see any study where people abuse the CES device. And also, as far as I know, this is a product that is available over the counter in other countries, and it's available by prescription in this country. But one of my concerns is, if this device is reclassified, the extensive cost to the manufacturer is going to push most of the manufacturers out of the market, in turn raising the cost of the devices that are on the market, that will stay on the market, making it unavailable to folks who need it the most.

A lot of folks who suffer from substance abuse don't have health insurance, can't afford the medications that are prescribed by their physicians on a monthly basis. As I'm sure you all know, you're psychiatrists and medical professionals, they're very expensive. The CES devices are affordable, they're effective, and the research I did, I did not find any major adverse effects from them.

So, on behalf of the patients that I see and the folks who are at the low end of this deal and suffer from addiction, please reconsider the classification of this device and keep it where it is.

Thank you very much.

DR. HURST: Thank you, Mr. Daggett.

Does anyone else wish to address the Panel at this time? If so, please come forward to the podium, state your name, affiliation, and indicate your financial interest.

DR. BROCK: Hello, I'm Dr. David G. Brock, Medical Director of Neuronetics, maker of the NeuroStar TMS Therapy System. My financial interest: I'm an employee of Neuronetics. And I would like to provide comment to correct some materials that I have seen provided to the Panel regarding TMS devices, particularly with regard to safety and efficacy.

As background, the NeuroStar TMS Therapy System was cleared by the FDA in October of 2008 for patients with major depressive disorder who failed to benefit from one prior antidepressant medication of adequate dose and duration in the current episode. NeuroStar TMS was studied in a large multicenter clinical trial, and FDA clearance was based upon this study of 301 patients. In the indicated study population of one prior antidepressant failure, there was a significant p-value and a moderate to large effect size.

Since FDA clearance there has been another large independent trial sponsored by the NIH, which has also shown a significant effect size with

the prior endpoint of remission.

Since that study there have been two large open-label trials, including a recently complete NeuroStar study of 300 patients, demonstrating 50% of patients reaching a clinical response and one-third reaching remission.

Finally, in clinical use of the NeuroStar TMS Therapy System in over 8,000 patients with over 250,000 treatments delivered, there's an excellent safety profile with the most common side effect associated with TMS being scalp pain or discomfort, with no systemic side effects and a rare incidence of serious adverse events with a frequency of less than .03% per treatment.

Thank you very much.

DR. HURST: Thank you, Dr. Brock.

Does anyone else wish to address the Panel at this time?

(No response.)

DR. HURST: Thank you. We'll now take a 20-minute break. Panel members, please do not discuss the meeting topic during the break amongst yourselves or with any member of the audience, and we'll resume 20 minutes from now.

(Off the record.)

(On the record.)

DR. HURST: There are three different petitioners presenting at this meeting. Each petitioner -- excuse me, could we have order, please?

Each petitioner will have 45 minutes to make their presentation before the Panel. We'll proceed based on the order detailed in the agenda. You may only approach the podium to address the Panel when directed by the Chair.

Our first petitioner will be Electromedical Products International, or EPI.

MR. ELDER: Good morning. My name is Scott Elder. I'm Vice President and General Counsel for Electromedical Products International, EPI. I want to thank you for the opportunity to speak with the Panel today.

Our presentation will focus on the Alpha-Stim CES device, which is the device manufactured by EPI. In addition to our PowerPoint presentation, EPI has provided this Panel with a point-by-point response to the 2011 proposed rule and a response to the -- a brief response to the proposed questions and Executive Summary FDA provided to us just 48 hours ago. Additionally, we've provided you numerous documentation prior to the meeting that you should all have.

Dr. Kirsch and I will be giving the presentation today on behalf of EPI. But as you see, we have a larger team with us, all of whom are prepared to answer any questions you may have.

Francine Nichols, who is listed as one of our panel members and helped prepare a large portion of the scientific evidence for this presentation, has had some health issues and is unable to join us today.

We'd like to begin this presentation with a brief overview of

Alpha-Stim. Alpha-Stim is a CES device which has been on the market in the United States since the 1980s. It is cleared to market by the FDA through the 510(k) process for the indications of anxiety, insomnia, and depression. U.S. sales are limited to by or on the order of a licensed healthcare practitioner. Elsewhere in the world, Alpha-Stim is sold over the counter and has Class II device status in Europe and Canada. An estimated 8.25 million treatments were administered over the last five years. Currently our largest customer is the United States government and state governments, followed by China and Europe.

As you can see in this slide, EPI's government orders have increased dramatically over the past five years. Currently EPI sells over 1,000 devices per quarter to the U.S. government, and our U.S. military market grew 57% in the past year, helping establish the effectiveness of the device.

The U.S. military's use of CES is primarily for anxiety, insomnia, depression, and PTSD. This graph also highlights a continual growth in utilization of Alpha-Stim CES with service members for those primary indications.

This chart provides numbers which were graphed for you in the prior slide, again highlighting a continual increase in utilization of Alpha-Stim CES over the past five years by the U.S. Department of Defense for the treatment of depression, insomnia, anxiety, and PTSD, which FDA acknowledges in its Executive Summary is a form of anxiety.

In 2010 the Pain Management Task Force of the Office of the Surgeon General for the U.S. Army listed CES as Tier II modality in its standard of care protocols, highlighting the acceptance of CES within the U.S. Department of Defense. Three colonels, who were a part of the task force, were users and prescribers of CES, and they were instrumental in CES' inclusion within the guidelines.

So, how does one now use CES? I'm now going to play for you, if I can do this, a video.

(Video played.)

MR. ELDER: That was a brief video taken from our training video that's provided to all of our patients upon the purchase of an Alpha-Stim CES device. It's a 30-minute training video.

CES has had a long history with the FDA, as this has been on the market since the 1960s in the United States. As a pre-amendments device, CES was placed in Class III until FDA could determine its proper classification. Since the 1970s, all legally cleared CES devices have been cleared through the 510(k) process of substantial equivalency. A CES is not life supporting or life sustaining, and evidence exists to determine that special controls would provide a reasonable assurance of safety and effectiveness. Therefore, CES does not fit within the Class III classification.

EPI has filed five separate 510(k) applications, one PMA, and two petitions for reclassification with FDA, all highlighting the safety and

effectiveness of the device. In August of 2011, FDA proposed a requirement that CES devices would go through a premarket approval process, and EPI submitted this petition for reclassification.

During our petition for reclassification, we submitted new information respecting the device, and based upon what the FDA indicated earlier through the reclassification process, this is new information that we would like you to consider today.

EPI is here today to ask that this Panel review the research and data provided to determine if there's a reasonable assurance of safety and effectiveness with CES, and if sufficient information exists to establish special controls so that CES can be down-classified to Class II.

Class II devices are subject to special controls, which include performance standards, postmarket surveillance, and patient registries. EPI will show today that it has sufficient special controls in place to allow for down-classification.

There are certain factors that are considered when determining the safety and effectiveness of a device. Factor 1 is the persons for whom the device is intended. The target population for whom CES was intended is defined with the federal regulations as those patients with anxiety, insomnia, and depression. The target population has been served by CES since the late 1970s.

Factor 2 are the conditions for use and the labeling of the

device. Alpha-Stim CES has been labeled and used for anxiety, insomnia, and depression since the 1980s.

Factor 3 is the probable benefit weighed against the risk of injury from use. Alpha-Stim CES has a very good risk/reward ratio, which is consistent across all research.

Factor 4 is the reliability of the device. EPI has 31 years of research, data, and inspection reports confirming the device's safety and reliability.

I'd like to also point out that we're compliant with ISO 13485 standards.

The reviewer of a reclassification petition is to rely upon valid scientific evidence to determine whether there's a reasonable assurance of safety and effectiveness. Valid scientific evidence includes well-controlled investigations, partially controlled studies, studies and trials without matched controls, case histories by qualified experts, and reports of significant human experience.

Given our time limitations today, EPI is focusing on Alpha-Stim double-blind RCT studies. EPI has also provided FDA additional studies that meet the definition of valid scientific evidence, and copies of these submissions have been provided to this Panel.

EPI is in a unique position where it comes to you today with 31 years of data establishing the safety of Alpha-Stim CES. The reality is that,

unlike FDA's proposed rule which discussed potential risk to health, the safety data provided to this Panel today will establish how safe Alpha-Stim CES truly is. There's virtually no risk with the device, as we will show that with 8.25 million treatments over the past five years, there were 15 consumer complaints, all of which were minor and self-limiting.

There's a reasonable assurance of effectiveness when it can be determined that in a significant portion of the target population, use of the device will provide clinically significant results. EPI has an abundance of well-controlled investigations amassed over 31 years of encouraging research by independent government and university investigators, in the form of mechanistic studies like fMRI, LORETA, EEG, EMG, and other diagnostic tests, double-blind randomly controlled trials and other less rigid models. This research is also supported by postmarket surveillance and comprehensive scientifically valid user surveys.

You will note several comparisons in this presentation to rTMS. EPI felt it was appropriate to use rTMS as a comparison because it was the most recent device FDA has classified as a Class II device, and rTMS is used as a treatment for depression. We agree with FDA that a comparison of CES to rTMS is valid. EPI has self-imposed special controls for nearly two decades, which compare closely to the special controls recently adopted by FDA for rTMS. EPI is compliant with FDA, European, Canadian, and Chinese regulatory agencies and many other regulatory agencies worldwide. Alpha-Stim CES is,

again, classified as a Class II device in Europe and Canada.

This Panel is charged today with the task of determining whether the evidence submitted and available is valid scientific evidence for determining the safety and effectiveness of CES. The valid scientific evidence, when taken as a whole, should provide adequate support for a determination that there is a reasonable assurance of safety and effectiveness. EPI's data provided today and in 2009 and 2011 submissions, when taken as a whole, provides more than a reasonable assurance that Alpha-Stim CES is safe and effective for the conditions of use of anxiety, insomnia, and depression.

Dr. Kirsch, who is the inventor of the Alpha-Stim CES and who introduced Alpha-Stim to the market, will now present data evidencing the safety and effectiveness of CES.

Thank you.

DR. KIRSCH: Thank you, Mr. Elder.

We usually talk about safety and effectiveness, not effectiveness and safety, so we'll start with safety. It just rolls off the tongue better.

First of all, we don't know who the anonymous people at FDA are who are hypothesizing side effects. Worsening of condition being treated. Well, everyone knows that every antidepressant doesn't work. That knocks that one out.

Potential adverse effects from electrical stimulation of the

brain. We've been in business 31 years with this technology, legally. There's no surprises coming up. The newer brand technologies, deep brain stimulation, TMS, VNS, these things are unknown long term. Alpha-Stim is not.

Potential risk of seizure. Just take that one off the list. It hasn't happened in 31 years. Why are we still rehashing hypotheticals from the 1970s?

Skin irritation, that occurs. As Dr. Earthman said, when you're treating a depression patient, they get a little bit of a rash on their ear, it's treated with a cortisone cream and it goes away the next day. So what?

Headaches do occur rarely, and they're self-limiting and mild. And blurred vision, cross that one off your list. It hasn't occurred.

So, let's get away from the hypotheticals, finally, that FDA keeps rehashing in my 30-year career, and let's talk about truth. So, now we'll talk about truth.

First of all, in 1974, the FDA commissioned, as another -- one public speaker said, commissioned the National Research Council in Washington here to review the safety of electrical stimulation to the brain, CES, and they determined that under 1 mA, that side effects are virtually nonexistent and there is no evidence to contrary since 1974. The highest output of our device is .6 mA, which is 60% of what the National Research Council considered to be safe.

Now, in the last five years, 2007 to 2011 -- and I remind you again, we've been in business 31 years -- we have sold 58,000 Alpha-Stims, and there were 15 reported side effects to us. Mostly skin irritation. A very strange one, black tongue. That turned out to be Pepto-Bismol. You live and learn.

We also do a lot of surveys, postmarketing surveys, of practitioners and patients, and we determined that using a very conservative estimate, 8 1/4 million treatments have been conducted with Alpha-Stim over the last five-year period and we had 15 side effects.

In addition, looking at every study that discussed side effects with Alpha-Stim, we did something that's very strange, we totaled the side effects and we got 2.47. Except they're not side effects. Of the 2400 people in these studies who actually received stimulation, there were 59 reports. However, when you subtract the normals, like oh, I feel the ear clips or I feel a little dizzy, as you just saw on the video, that's normal for this. You're supposed to turn up the current until a slight vertigo, like rocking on a boat, is experienced, and then you turn that back. That's the eighth cranial nerve, which happens to be in the pathway of the stimulation.

And so when you subtract out those, it's less than 1%. This compares favorably with TMS. And I know there was somebody who said that our TMS information is wrong. It is not wrong. It is taken from the FDA's presentation on TMS, which appeared that the FDA has stock in TMS, if you

read that transcript.

Anyway, they had more than half the people have a headache. We don't have anything like that. We use a very, very low current.

So, as far as serious side effects goes, in 31 years on the market we have none. Absolutely zero. So, I think it's past time we should be talking about fabricated, potential, theoretical, hypothetical, or fictional side effects. Let's talk about reality. If a drug's on the market 30 years, you don't start to speculate what it might do, and we deserve the same. So, this compares favorably with TMS as well, which did have a few, although not too many, major side effects.

All right. As far as effectiveness goes, we're only talking about CES. We do agree with FDA and Dr. Rosch that there's no class effect from CES. The stimulation parameters are different. The FDA is talking about, because of that, you can't establish special controls. I don't even understand that. Does one antidepressant drug have to account for another one? It doesn't make any sense. The fact is our technology works. Another company needs to prove that their technology works.

And when they say that substantial equivalence does not require clinical trials, that is not true in our case. We have the evidence to prove that our 510(k), original 510(k), took 22 months and required repeated evidence of efficacy to establish it as substantially equivalent to pre-amendments devices. They always made us prove that our technology

works.

All of our studies were independently conducted. We haven't funded any of the studies. We just hoped for them. We do loan the devices for the research and typically -- well, not typically -- dosage equals current inversely proportional to time, which means the higher the current, the quicker the treatment. So, for research we turn it way down so you can't feel it, and the normal 20-minute treatment is conducted in an hour.

This is a flowchart of how all the RCTs I'm about to talk to you about were conducted. Basically what we see here is that the device is locked in the parameters of a longer time and a low current. The subjects are randomized, as per the protocol, into the active or the sham group. And this is just as good as a sugar pill, a placebo pill in a drug study, because you don't feel anything. You see the device count down. It all looks the same. The only difference is the serial number, and that could only be determined by the key that we present to the -- usually the IRB, in a sealed envelope. And some groups have a third usual care or wait line control group, and some groups have a crossover arm of the study.

I don't know what happened to the top of this slide. Something happened here. It says up here, where you can't read, but you have copies, EEG changes in 30 subjects treated with a single 20-minute treatment of Alpha-Stim CES. And basically this was done at the University of North Texas. Here's the nose, here's the ears. It goes from blue is less to red is more, and

on traditional EEG groupings we see less delta and more alpha, which means you're more alert and more relaxed. This is the effect that people report from a simple 20-minute treatment.

There are three Alpha-Stim CES devices here. Here's what one looks like. You're welcome to play with it; you're welcome to put it on. It won't hurt you. Don't worry about it. It's perfectly safe. You become relaxed.

Okay. So, these are RCTs in anxiety. I'm going to go through these. Dr. Kim did a study on preoperative patients, and if any of you have ever had any surgery or seen anybody have any surgery, you're probably seen that it's anxiety provoking. And so he found significantly lower scores at the end of the -- I mean from before and after the treatment, that the p is less than .01 level and a large effect size. As a reminder, Cohen's, the effect sizes, .2 is a small effect, .5 is a medium effect, and .8 is a large effect. He also found lower blood pressure in his patients, an objective measurement.

Dr. Strentzsch did a study on chronically mentally ill partial hospitalization patients who are usually excluded from this type of research because -- of course they all have anxiety issues or they wouldn't be on this chart, but they also have major depressive disorder, bipolar disorder, schizoaffective disorder, and schizophrenia patients. And she found significant results of p equals .02 with a medium -- sorry -- with a small approaching medium effect size.

Dr. Cork and Dr. Lichtbroun did virtually the same protocols, a six-week study with two three-week arms, the first one being a randomly controlled trial and then a crossover to an open clinical trial, and they both were done on very severe pain patients who had anxiety, and they both had significant effects in the primary measures. Dr. Cork saw anxiety significantly improved at the level of p is less than .01 and Lichtbroun at p equals .02 at a medium effect size.

Dr. Winick had a study very similar to Dr. Kim, except not only was it preoperative, but it was intraoperative during dental procedures, and this had both the dentist and the patient look at the anxiety levels, using two different scales each, before, in the middle of, and at the end of the procedures, and he found significant effects in all measures by both the dental observer and the patient.

Dr. Voris saw psychiatric patients who had significant effects at the p equals .0001 level with a very large effect size, 1.60. That's more than a full standard deviation. And they also had the similar results in objective measures.

There was one failed RCT study in anxiety. However, this was state anxiety, the anxiety you're experiencing now, like when you're presenting to an expert panel for FDA, or when you're waiting in traffic, you're stuck in traffic, or when you're at the dentist. Or a preoperative patient would have this, as well. State anxiety, the anxiety I'm experiencing

now, as opposed to trait anxiety. Personality trait chronic.

So, this anxiety was measured a week after the final treatment, which basically created a washout period. However, Dr. Mellen has published six studies through the University of Alabama and within the Alabama prison system, where it was used extensively.

Now, confirming these RCTs are some very well-controlled open-label trials by experts in the field. The first one, Dr. Bystritsky at UCLA runs the anxiety disorders clinical at UCLA and is one of the leading anxiety specialists in the world. In fact, he recently published an anxiety study in the *Journal of the American Medical Association*, based on a $20 million government grant. And he also lectures at APA regularly.

And so he did a study and he determined that anxiety scores decrease significantly on HAM-A at the p equals .01 level and a very large effect size, 1.52. And that was on the HAM-A. And then the four-dimensional anxiety and depression scale also had very significant results at p equals -- sorry -- p is less than .01 and d equals .75.

This is his chart, which he was kind of enough to loan me for this presentation. Not my chart. This was presented at the American Psychiatric Association in 2009 and published in the *Journal of Clinical Psychiatry*. You can see the anxiety going down very clearly from this chart over the six-week period. And Dr. Bystritsky, who I failed to mention, is also a full professor at Harvard, did manage -- did compare this to results -- he

found the results similar to that found in clinical psychopharma trials.

Dr. Overcash did a study for an HMO in Pennsylvania and found that the ratings of anxiety were significantly reduced in his patient population, at the p is less than .05 level, as well as on objective measures. So, he used psychometric and physiological measures.

So, when we look at all of that data pooled, we can average a .9 effect size, which is a large effect size, from these studies and a .79 effect size from the physiological measures, which you might round to .8, and that makes it large.

Moving on to insomnia studies, we have Dr. Taylor at the University of Virginia and Dr. Lichtbroun, who we've already discussed, at Robert Wood Johnson Medical School, looking at insomnia and fibromyalgia patients, who are notorious for not being able to sleep. And Dr. Taylor found very significant results over an eight-week period.

Here's her graph from her about-to-be-published study. So, the active group, but not the sham group and not the usual care group, had achieved significant results of p equals .0001 and an effect size, a small effect size of .3. And her patients completed the study -- I mean subjects -- with scores below the range of insomnia.

Dr. Lichtbroun did a double-blind study where most of the patients -- the blue line here represents most of the patients going into the study had sleep problems, over here, and very few of the patients had good

restful sleep, and at the end of three weeks you see virtually a mirror image of those results. People were able to sleep. Only 5% of the people going into the study were able to sleep, and it was about 5% of the people, or less, going out at the end of three weeks that had sleep difficulties.

Dr. Mellen, who we saw had failed the state anxiety study that was -- because the measures were taken a week after the end of the study, did find significant effects in sheriff's jail security and patrol officers in the State of Alabama, where the CES group had significantly less depression than the sham group on both the Beck Depression Inventory and the Brief Symptom Inventory for Depression. And Dr. Bystritsky's group at UCLA had good effects on the HAM-D scale at p is less than .01.

As well, we have checked last week, and we have 27 studies of Alpha-Stim right now underway throughout the world. A lot of people call me a data junkie. I love research.

And so these are the studies underway right now that are being funded by the United States government. And these are all on anxiety, depression, insomnia, or at least one of the above and perhaps some other things. And the first four are being done by the United States Army, our biggest customer, and one is being done by the DeBakey VA in Houston, in conjunction with Baylor University. The final one is being conducted near here, Virginia Commonwealth University, VCU, and it's funded by the National Cancer Institute of the National Institutes of Health, and it's primarily on

depression in breast cancer patients. And, of course, it's also anxiety and insomnia because these are common comorbidities. These things tend to function as a group.

Okay, important for the next aspect of our presentation is this finding that was published in the *Journal of Clinical Epidemiology* a few years ago that said one single question on a Likert or a VAS scale, which the FDA is trying to throw out as being irrelevant -- actually, they threw out all of our studies for little bureaucratic technicalities. We ask you to be less biased and more objective in your analysis of truth.

And so here we see a single question correlating well with the state-trait anxiety index, which is the most validated test in anxiety. It's not the HAM-A, it's the STAI, Spielberger's test. And this was correlated at the 95% confidence interval.

Keeping that in mind, we have done surveys. We constantly do surveys. Everybody who gets an Alpha-Stim gets a survey. I mean, they don't all respond, but they all get a chance to.

So, this is a military service member survey and a civilian survey. The blue bar, the third bar down on these three, anxiety, insomnia, and depression charts, the blue one is service members and the one below that, the purple one, is civilian survey. And this is the people who are reporting an effective result, and it compares very favorably to drugs that you all are aware of because these are blockbuster, major drugs used in these

indications. And that comes from a WebMD ongoing survey that we accessed here in October of last year.

So, for anxiety, it compares well with Xanax and Ativan; for insomnia, Lunesta and Sonata; and for depression, Zoloft and Wellbutrin. It not only compares well, but in some cases a little better than these drugs.

And you have a copy of this entire survey. In fact, it's on the cover of this book we gave you, and I urge you to look at this book. The FDA says, oh, don't look at that, that's just anecdotal. But that's people who use it. I don't think the FDA reviewers, whoever they might be, are using this or ever seen a CES device. So, read this. You have colonels in the Army, you have one general, and you have a priest, a chaplain. You have all kinds of people who use this, who are qualified. Lots of psychiatrists in here. So, read that, please. Look at them.

So, this is the most stringent measure of clinical importance that we could find in the literature. According to Dworkin, 30% to 49% is considered of moderate clinical importance, and greater than 50% improvement in a patient is considered substantial clinical importance. And here you can see that we met the criteria of substantial clinical importance in all the areas. Because this was a military survey, we called out PTSD; however, that is an anxiety disorder as well.

And I don't know what happened to these slides. My slide doesn't look like this. But this one says 60% of the civilian population -- this is

annoying. You have white copies that we gave you, hard copies. But this says that 60% of the 1745 responders to a civilian survey improved at least 50%. So, that confirms the last slide. All of this information is cross-confirming.

And this is the comparisons of effectiveness data at p-values with TMS. Again, this information comes from the FDA Executive Summary to this Panel in 2007 that we pulled off of the FDA website. So, these numbers are absolutely correct.

We have given you six RCTs in anxiety. We've seen p-values between .0001 to .02. This was confirmed in open clinical -- well-conducted, open clinical trials, which meets the definition of valid scientific evidence in the Code of Federal Regulations. And those results are p equals .01 to p is less .05.

This compares favorably with the data from TMS. The original finding of the first arm of their one three-arm study showed minimally clinically interesting differences between the treatment groups, and their results were p equals .057. However, when four of the active and two of the sham subjects were thrown out and there was a reanalysis done on the statistics, they did achieve significance, and they did achieve significance on secondary measures. And I do agree that they've achieved significance since then in other studies.

So, when we looked at the pooled effect size, we can see that ours is .91, which comes from the previous slide that you've seen, and this

compares favorably with the small effect sizes, small to medium. This slide somehow got corrupted since we've sent it to FDA, but that says medium down there and that, basically, ours is small, medium, medium, medium, large, very large, and very large. Theirs is small, small, and medium. And so again, it compares favorably with TMS.

And the reason we're harping on that is because this Panel reviewed TMS in 2007, and the FDA classified it as Class II in the *Federal Register* July last year, one week before they treated us the exact opposite way. So, they're being arbitrary and capricious about this, between these two technologies.

So, based on the Alpha-Stim research that I've just presented to you, when taken as a whole, which is in the regulations, that wording, when taken as a whole, you're supposed to look at it when taken as a whole. The 10 studies that I just presented provide significant results, supporting a finding of reasonable assurance of safety and effectiveness. That's your job here today.

Alpha-Stim is safe and effective for the treatment of anxiety, insomnia, and depression. And these conditions are ubiquitous in all patient populations. Patient population is meaningless. Since August of last year, I've talked -- every psychiatrist I've talked to, and I've talked to several a day, I've asked this question to, and not one said you're wrong. Every single one said you're right, there is no distinction in patient populations for these three

conditions.

When you go to the dentist you have anxiety. I'll bet some of you have been to the dentist and have experienced that. Did you ever notice how hard you're holding the chair? That's anxiety. All right.

So, adverse effects were mild and self-limiting in all our studies and across all the information for 31 years. So, there won't be any surprises. A PMA is not going to accomplish a thing, except put a huge burden on my small company.

Now, I would in some ways prefer a PMA, but I have a PMA pending at FDA since 1995, and they treated us horrendously about it. They only met with us once, and at that time, the director of the Office of Device Evaluation for Centers for Devices, CDRH, said that there are no safety issues. So, again, I think you can just put that one to sleep.

Why isn't the FDA today talking about what the head of the Office of Device Evaluation said in a 1996 meeting, I believe, as opposed to what the panel is chatting about in the 1970s, before I was in business for 31 years? We should talk about truth and reality.

Okay. So, we have significant effects. We have no serious or hardly any adverse effects to speak of whatsoever. It's sold over the counter outside this country, everyplace else in the world where it's been approved. And don't think it's easy to get approved in other places, and don't think that general controls are easy. The FDA comes into our office every two years,

Europe comes in every year, and these are not fun times when they come in to inspect us. Europe works with us. FDA works against us. They're looking for aha, I got you. But we're still in business even though we've had these inspections all this time.

So, today we have seen that there's reasonable assurance of safety and effectiveness for Alpha-Stim CES and no evidence of the contrary in 31 years of marketing, with well over 10, probably more than 20 million treatments administered. Therefore, we respectfully request that you recommend down-classification of Alpha-Stim CES for the conditions of anxiety, depression, and insomnia.

And I thank you for your time, and I look forward to your questions because I wish I had three or four days to spend talking to you about my life's work, 30 years. One day per 10 years seems reasonable. Forty-five minutes, I hope I've educated you. Thank you.

DR. HURST: Thank you very much.

Before our next petitioner, which will be Fisher Wallace Laboratories, Dr. Eydelman would like to make a comment.

DR. EYDELMAN: I just have two comments. First of all, I'm sorry you experienced some problems with the projection of your slides. I believe we have warned you that, due to the difference in the software, if you use an FDA computer, there might be an issue, and I think that's what you experienced.

Second, I want to point out that I believe Dr. Kirsch misspoke during his presentation on Slide 15 when he stated that he agrees with FDA on the appropriateness of comparison of CES to rTMS. FDA has never made that statement. As a matter of fact, Mr. Marjenin in his presentation on Slide 8 -- 6 specifically delineated the differences between CES and other technologies and clarified that this discussion should be limited to CES.

Thank you.

DR. HURST: We're going to have time later for a reply.

DR. KIRSCH: Well, one minute, quickly, if I may.

DR. HURST: Not at the present time. We will have time later for a reply to that, as well as for additional questions.

Our next petitioner, please, Fisher Wallace Laboratories.

MR. FISHER: Good morning. My name is Charles Fisher, and I'm President of Fisher Wallace Laboratories, a leading manufacturer of CES devices. It is an honor to present our reclassification petition to such a distinguished Panel.

Thirty-five years ago this Panel recommended that CES be designated as Class II for the treatment of anxiety in substance abuse patients. Today we are asking the Panel to recommend Class II designation for CES when it's used to treat substance abuse patients who have failed on drug therapy or cannot tolerate drug therapy. We are not proposing a new intended use for CES. Rather, we are focusing on a subset of the population

already being treated under the current indication.

Many small but well-controlled studies have been performed on the substance abuse population, and we will present statistical analysis of that and the research shortly.

I respectfully ask the Panel to apply the precise definition of valid scientific evidence. We are confident that the evidence we are providing today fully meets that precise and comprehensive definition.

The FDA is concerned that the special controls we have identified do not address an underlying issue, namely, that there has been no systematic attempt to determine a set of stimulation characteristics that are necessary for effectiveness. We must be clear on the following regulatory fact. Determining the set of stimulation characteristics for all current and future devices is not necessary for classification in Class II.

Just as the Agency did for rTMS last year, placement of CES in Class II can be based on what is known about today's technology. For new devices that have characteristics that differ from existing CES devices, the FDA has the ability to get whatever data is sufficient to ensure that they are as safe and effective as existing devices.

With rTMS the FDA classification classified one device and one set of specifications in Class II with special controls that were sufficient to ensure that new rTMS devices would be as safe and effective as the single device that they allowed to go to market. The model established for

regulating rTMS in Class II is equally applicable to today's CES devices as well as new designs that may be proposed in the future.

Our position is that there is valid scientific evidence that establishes that our CES device, as well as others, is safe and effective for the proposed indication.

The maximum amperage for CES devices has for decades been 4 mA. Four milliamps is too weak to injure a patient and is well below the seizure threshold. CES devices employ an alternating current, which contributes to the fact that they do not cause electrode burns. CES devices are also battery powered, which helps ensure their safe use.

Our proposed indication for Class II focuses on a subset of the general population. We do not intend for CES to be prescribed at the exclusion of conventional therapy. Comprehensive device labeling adequately mitigates this risk, and we have built that safeguard into the wording of our Class II indication.

Class III is typically reserved for life-sustaining devices and devices which can cause illness or injury. Many Class III devices are surgically implanted. CES is not life sustaining, and there's no credible evidence that CES causes illness of injury.

rTMS was granted Class II status last year. rTMS is a safe technology that generates an electrical charge in the brain that is 10 to 100 times more powerful than CES.

The special controls and guidance documents created for rTMS are an appropriate model for CES. I'd like to emphasize that CES has been on the market for more than 40 years. Extremely few adverse event reports have been filed, and none of them provide evidence that CES was actually the cause of the reported discomfort.

Over 500 psychiatrists prescribe our company's device. The chief of psychiatry at Mass General Hospital, Dr. Jerrold Rosenbaum, prescribes and submitted a letter to the FDA in support of Class II designation. The same is true for the retired chairman of psychiatry at NYU, Dr. Robert Cancro. Dr. Richard Brown, a Professor of Psychiatry at Columbia University, has prescribed our device over 450 times, with excellent results for his patients.

Every doctor that prescribes our device appreciates that we offer a 60-day refund policy, as do many of our other competitors. Only 12% of the devices purchased from us are returned for a refund, from the patient.

Through decades of safe and effective use, CES has transformed from an outlying therapy into one highly regarded by the psychiatric community.

CES is prescribed at Army, Navy, and VA hospitals. Dr. Dallas Hack, the director of the Combat Casualty Care Research Program for the U.S. Army, has officially requested that the FDA perform an expedited review of CES reclassification. He's also formerly expressed the Army's desire

for CES devices to remain available to treat soldiers.

CES manufacturers like Fisher Wallace are small, high-growth companies that cannot at this time afford the burdensome PMA process without having some ability to market our devices through reclassification.

We look forward to answering any questions you may have regarding the special controls needed to ensure safety and effectiveness of CES going forward.

And I would like now to present -- to turn over the presentation to Dr. Richard Chiacchierini, who will provide a biostatistical analysis of our research.

Thank you very much.

DR. CHIACCHIERINI: Good morning, distinguished Panel members. I am Dr. Richard Chiacchierini. I'm the former director of the Division of Biometric Sciences for CDRH/FDA, and currently I'm a statistical consultant to the medical device industry. I have no financial interest in any sponsor involved with CES, except for my consulting relationship, and I have been engaged by Fisher Wallace to review the articles of evidence of effectiveness and safety for CES.

About 40 articles have been provided to me by Fisher Wallace, and they included many types of studies, single-arm trials, randomized trials, and literature reviews. The articles I am going to present today are those that, in my opinion, provide the highest level of evidence: randomized trials.

All of these were included in the FDA review.

Slide, please.

One common theme consistent with what FDA said in their review is that almost all of the studies in the literature are small. The study sizes range from 10 to 64 subjects. They had involved different populations, drug and alcohol withdrawal, psychiatric disorders, and insomniacs, and with different CES exposures. Most of these populations are difficult, with sometimes very high compliance or dropout rates.

The reviewed studies include six studies, randomized studies, in humans and one animal study to support effectiveness. There were two randomized studies that failed to show effectiveness. And there were three non-randomized studies to indicate biomarker changes.

Now, unlike negative studies, positive studies that are small do not have statistical power implications. It's the other side of the curve that you're worried about, and that's Type I error. But there are consequences of small size with regard to comparability adjustments that you might be able to do.

The statistical analyses in these studies were not always complete, but appear to be representative of the journal and the year of publication.

Next slide, please.

The first study I would like to discuss involves insomnia. There

were only 10 people in this study, and one might say, well, how can you gain anything from 10 people? Well, these people were very well matched, they were randomly provided to either CES or control. And the evaluation was done in a sleep laboratory, and that's the highest level of evidence that you can have. And the evaluations of the primary endpoint, which was latency to sleep, were done objectively by a blinded evaluation of the EEG, not a subjective measure.

So, the baseline characteristics appear to be balanced, but the tests are likely underpowered, as I said before. However, 24 15-minute daily treatments demonstrated reduced sleep onset latency and time in bed awake after sleep onset in CES cases, but not in the sham, by the blinded EEG observation. There was no report of adverse events, and we'll see the results in the next slide.

As you can see, typical of most of the studies, the studies were compared statistically this way, but were unusually compared this way. I did a post hoc analysis of these data because there was sufficient information, the mean standard deviations and so forth, and as you can see, if you do the cross-treatment comparison, there is statistical significance in both onset latency and total time in bed awake after sleep onset for this study.

Next slide, please.

The second study involves a randomized, one-to-one, double-blind study of 20 habitual alcoholics with non-alcohol withdrawal syndrome

effective disorders, who were alcohol abstinent for three to four weeks. This is a study by Krupitsky. There was balance in baseline characteristics, except patient age. They were slightly older in the CES group. Thirty-minute exposures daily for four weeks showed strong statistical significance in favor of the CES group in Zung's depression test, reactive anxiety test, the Taylor anxiety scale, and the MMPI depression scale.

Also they did a measure of the biomarkers and MAO-B activity and GABA activity were elevated in the CES arm but not in the control arm. There was no change in serotonin, dopamine, or beta-endorphins, and there was no report of adverse events.

Next slide.

As you can see the results here in this particular study, the statistical tests were done between treatment groups by the authors, and it indicates the amount of change and the degree of difference that was observed. And these are both statistically and clinically significant.

Next slide, please.

The third study involves a three-to-one randomized, double-blind study of 40 patients with alcohol or poly-drug abuse with anxiety, with no psychotropic drugs use during study. No analysis of baseline characteristics and no discussion of the study completion rates were provided for this study. However, 15 30-minute sessions over three weeks showed strong reduction in state-trait anxiety indices and the profile and mood

states, the POMS survey, among CES but not among sham patients. There's no difference in response between older and younger subjects and between alcohol and drug abusers, and there were no report of adverse events.

Next slide.

In this study, the statistical analysis was not provided, the p-values were not provided, but the decline from baseline to the post-baseline measurements indicate a statistical significance, in the words of the authors.

Next slide, please.

The fourth study to support effectiveness was a randomized one-to-one, double-blind trial of 21 psychiatric inpatients suffering from depressive disorders with no active drug treatment during stimulation. Baseline characteristics were not significantly different, but I must say that the point estimates were not close for some variables, including age, gender, and length of illness. Two 30-minute treatments over five days showed significant declines in anxiety and increases in awakening time in CES patients, but not controls, during the five-day withdrawal period from the drugs. There was no report of adverse events. There were no direct comparisons of differences from baseline, nor could they be done from the data presented.

Next slide, please.

You can see here, typical of these studies, the comparison of

the treatment groups over time. This is statistically significant, this is not, and this is statistically significant, this is not.

Next slide, please.

The fifth study involves 28 former heroin addicts undergoing treatment for methadone withdrawal. And this is an interesting study because they had the test arm and two control groups, a sham and a non-sham control. The balance of baseline characteristics was not tested, but anxiety scores were provided, and the baseline anxiety scores appear to be the same. Ten 30-minute sessions over 14 days demonstrated significantly reduced anxiety levels by the Taylor scale and dramatically reduced methadone intake in 13 of the 14 CET subjects remaining, but no change in either control group for anxiety levels.

Go to the next slide, please.

There were no reports of adverse events in this study, either.

Next slide.

An important factor here is one of the measures was return to normal anxiety. In the test arm there were seven people who had returned to normal anxiety, and in the control there were zero people who had returned to normal anxiety. And a post hoc Fisher's exact test done by me, two-sided, indicates a p-value of .006 for that relationship.

The continued methadone use was very interesting as well. There were nine members of the CES group who had ceased methadone use.

None of the controls had ceased methadone use. And this was significant by the same method with a p-value of .006.

Next slide, please.

Now, there are two studies indicated lack of significance. In the first study there were 28 psychiatric outpatients on reduction of symptomatic days and symptom sensitivity. The study was designed basically as a five-day treatment period, and they've measured the patients at 5 and 19 days after the cessation of treatment, thinking that the effect may have some sustainability. It was interesting to note that there was no difference in the two groups for symptom-free days on day 5 or day 19, but a secondary variable recording whether symptoms bothered subjects was significant in favor of CES on day 5, but not day 19.

The relevance of the endpoints, especially long after cessation of treatment, is questionable because it's my belief that you have a treatment to the brain, and once you cease that treatment, there's no permanent effect that you might expect from that. And so the 19 day is questionable. There were no reports of adverse events in that study.

Next slide, please.

In the second study that showed lack of effectiveness, it was a randomized study of 25 cocaine and 18 opiate male subjects during withdrawal. There was no analysis of baseline characteristics, and the patients appear to be on methadone during the trial. Continuous exposure

for 7 to 10 days failed to show statistically significant effect of CES on withdrawal scales. However, all sham subjects received a low level of current thought by the authors to be incapable of producing an effect. And there were no reports of adverse events here.

The authors do admit that the sham exposure could be therapeutic and that the measurement questionnaires may be inadequate to detect changes in withdrawal symptoms in this population.

Next slide.

The study of human -- we skipped the animal. Did we skip the animal study? We've skipped the animal study.

MR. FISHER: I have them in another thing. Hold on a second.

DR. CHIACCHIERINI: Okay.

MR. FISHER: We have time.

DR. CHIACCHIERINI: Well, basically, the animal study indicated two animal studies that were reported in the same report. In those reports, the first one was a 21-rat randomized study -- yes, there is it -- that indicated that the -- in the first 21 patients, they were looking at the effect of morphine while the rats were on morphine.

The first group of rats got CES prior to the second of third week of weekly morphine injections, and the other half were given CES on the third of third week injections, and then they measured a tail flick test. Both groups, while they were on CES, had a longer, three times longer tail flick

time than the non-CES animals, indicating a potentiation of the morphine effect.

In the second study there were 20 rats randomized to CES and sham exposures continuously for four days, and then they withdrew the morphine. The Gellert scale withdrawal scores were significantly lower in CES groups compared to the controls, especially on the maximum day of withdrawal, day three.

Okay, let's move on to the biomarker studies.

Now, there are three biomarker studies that were involved in this evaluation. In the first one they had human volunteers that were exposed to three different sets of stimulation over several days. They showed an increase in serotonin and a decrease in tryptophan.

The second group had serotonin and beta-endorphin changes in cerebrospinal fluid and in plasma in five volunteers, and there were beta-endorphin and melatonin reductions in plasma shown in 10 volunteers. That included the five volunteers in the prior study.

And in the third study there were 11 severely depressed subjects compared to 14 normal subjects and 23 chronic pain subjects, and there was a reduction in the serotonin levels in the depressed patients.

Next slide, please.

And these are the results of these studies. This shows you the Liss and Liss results that shows an interesting result. The TENS stimulation

did not show any effect on the substances, but the electric stimulation, whether peripheral or transcranial, showed a substantial change in these results

Next.

And, finally, these are the 11 severely depressed patients, and these are the p-values provided by the authors, of the changes in serotonin and cholinesterase.

Next.

So, basically there is evidence in the literature of effectiveness. You have to admit the limitations of the studies. And there were both human and animal studies which show effectiveness, and there are also biomarker studies that show that there's something happening in the blood or in the spinal fluid of the patients. There are no reports of safety events in any of these studies. I can't say that there were no events, just that there were no reports of events.

And that concludes my conclusion. I'd like to turn this over to Dr. Rosenthal.

DR. ROSENTHAL: Good morning. I'm Mitch Rosenthal, and it's a pleasure to appear before this distinguished Panel.

As a physician and psychiatrist, I've been engaged in the treatment of substance abuse since 1958. I've been a White House advisor on drug abuse, a special consultant to the Office of Drug Control Policy, and I

chaired the New York State Advisory Council on Drug Abuse for 12 years. I'm a lecturer in psychiatry at the Columbia University's College of Physicians and Surgeons, and the founder of Phoenix House, one of the nation's leading not-for-profit substance abuse agencies with some 150 programs in 10 states, treating more than 16,000 substance abusers every year.

Let me state, I receive no compensation from Fisher Wallace, nor do I have a financial interest in that company or any others that manufacture CES.

It is my opinion that the panel's 1977 recommendation of Class II status for CES, when it was indicated as a treatment for substance abuse, was an appropriate finding despite its reversal the following the year. Moreover, all the evidence we've acquired since that time should reinforce our belief in the safety of this technology and provide considerable indication on its effectiveness.

SAMHSA's finding that more than 23 million Americans are in need of treatment for drug and alcohol abuse makes a powerful argument for increasing therapeutic options available to clinicians and programs like those at Phoenix House and hundreds of other programs across the United States.

While I would not suggest that CES by itself should be the only form of treatment, I believe it can add meaningful adjunctive value to treatment, particularly when other means of dealing with client anxiety, depression, or insomnia are not working or inappropriate.

There is in the study submitted with the reclassification petition considerable evidence that CES impacts these substantive issues in substance abuse treatment. Depression, anxiety, and insomnia are common symptoms for substance abuse patients, especially during the early stages of treatment, and they are symptoms that are often difficult to treat.

Unless you've provided treatment or been in treatment, it's difficult to appreciate just how great a challenge these symptoms pose. CES can be used in conjunction with drugs as well as with patients who have been resistant to drug therapy or cannot tolerate the side effects of drugs. In other words, CES is a safe and valuable tool in the medical toolkit. It's a tool I would like to see remain available.

Our experience with CES at Phoenix House was a positive one. The treatment was made available to medically stable clients in the induction phase of treatment. The overwhelming number of reports we received from the 99 patients who volunteered to try CES were positive.

More significantly, retention was greater for this group. Clients who took part in the CES program were more likely to remain in treatment longer than those who did not. Retention and longer lengths of stay in treatment, as you know, are highly correlated to successful outcome.

Few clients reported a negative experience, and only four told us they were quitting on the CES program. The most common post-stimulation reports were I liked it, it helped me. Of 178 such reports, there

were 73 reports of liking the experience and 67 of finding it calming and 47 equally positive when citing such benefits as improved sleep and reduced anxiety.

What is perhaps more pertinent to the issue before this Panel is that among the 190 reports we received, there were only 3 reports of any discomfort, and all were minor. This finding would seem totally consistent with CES' more than 30-year history of safe use by substance abuse patients.

I find no reason to deem CES a risky technology deserving the Class III status it now holds. I'd urge the Panel to give CES its due and acknowledge low risk and evidence of benefit with a recommendation for Class II status.

Thank you.

DR. XENAKIS: Good morning. Thank you for this opportunity to speak to the Panel. My name is Steve Xenakis. I'm a psychiatrist, a former Army brigadier general, Medical Corps officer. I served on active duty for 28 years. I have a part-time clinical practice and consult with the Department of Defense and other government agencies on neuropsychiatric conditions.

Fisher Wallace has compensated me for my advice and assistance in their application for reclassifying the CES device. I'm a member of their medical advisory board. I do not own any stock in the company. My remarks refer specifically to the benefit of CES to soldiers and veterans.

First slide, please.

These are the figures for your consideration of what the size of the problem is here, regarding the scope and challenges that we as military physicians face after nearly 10 years of war.

The invisible wounds include the spectrum of emotional disorders, from post-traumatic stress to psychosis, mild traumatic brain injuries secondary to IED blasts, sleep disturbances, musculoskeletal aches and pains, substance abuse, suicide, and other related conditions. The impact of invisible wounds on the readiness of the military, burden on the Veterans Administration, and consequences to the nation are obvious.

Next slide.

The typical soldier or veteran seeking treatment for invisible wounds, abuses, or inappropriately uses alcohol, prescription medications, or illicit substances, suffers with sleep problems and musculoskeletal aches and pains, cannot control mood swings or anxiety and presents a risk for suicide or other life-threatening behavior. The number of service members and veterans who need treatment exceeds the availability of clinical services.

The range of current treatments for the neuropsychiatric conditions and associated invisible wounds of combat has been uneven or limited across the board. Most treatments only work some of the times and only modestly better than chance. Simply stated, we have few, if any, clearly effective treatments for many of these conditions.

From the standpoint of the average practitioner, which I

consider myself, I want you all to consider the following data points.

Regarding alcohol and substance abuse -- I think it's the next slide -- we've recognized that at least half of our soldiers returning from combat, during their interim year between deployments, probably engage in binge drinking and alcohol-related problems, are extremely significant. There is an increased risk for the Reserve and Guard and an obviously increased risk in our younger age groups.

Next slide.

For PTSD, veterans and civilians with complex PTSD are especially resistant to medication. No medication, by the Institute of Medicine, has been shown to have significant effectiveness. Antipsychotic medications that are commonly prescribed are not effective and have serious side effects, and few, if any, complementary treatments have been proven acceptable according to standards in some clinical trials.

Next slide.

The signature wound of these wars has been termed the IED blast concussions. There are overlapping symptoms with PTSD of irritability, affective lability, fatigue, sleep disturbance, and impaired cognition. DoD only recognizes cognitive rehabilitation as an accepted treatment. The IOM, on the other hand, has assessed cognitive rehabilitation therapy for mild traumatic brain injury as only marginally effective.

Next slide.

Pain and pain relievers, as you've heard, are a significant factor in the health and welfare in combat effectiveness of our troops. It is the most common disability and contributes significantly to alcohol abuse.

Next slide.

Some gaps in our clinical care and research for us to recognize. Medications do not help a significant fraction of our patients. About 25% of patients do not respond to SSRIs. Less than a third of depressed patients achieve remission within eight weeks. There's a high noncompliance amongst drug and alcohol abusers, and medications are probably over-prescribed for sleep and pain disorders.

Next slide.

There are few, if any, solid treatments for the symptoms arising from blast concussions. We face serious challenges in treating soldiers and veterans. The studies by the IOM regarding PTSD and mild concussion essentially found no demonstrably effective treatments. Many soldiers and veterans do not seek care because of an aversion to medications and seeing psychiatrists who only prescribe drugs. Most soldiers and veterans suffer from comorbid conditions of anxiety that includes PTSD, depression, insomnia, pain, and substance abuse, for which CES is indicated. Offering CES does not deny patients availability to commonly used treatments, but offers them an adjunctive and alternative that many seek.

Next slide.

CES is safe, practical, necessary, and effective. As a senior advisor to the former Chairman of Joint Chiefs of Staff Admiral Mike Mullen, I was his advisor for several years and I applied some principles for assessing promising treatments and getting them into the field expeditiously.

Remember, we have been at war for over 10 years, and many of us who served during the Vietnam era have been committed not to see the problems that followed that long war happen again.

These principles are safety, efficacy, practicality, and cost benefit. Regarding safety, these devices have been used for more than three decades, as you've heard. There's no record of significant or dangerous adverse events, including seizures. There are no serious side effects caused by CES. And the incidence of minor side effects, such as headache and skin irritation, is low and the effects are transient.

At times over the past 30 years, the FDA has lumped CES with other electrophysiological devices such as ECT and rTMS. We recognize, for this hearing, they have made a distinction. But as you've also heard, CES is much safer than either ECT or TMS.

The next slide, in terms of efficacy.

As noted, no treatments for PTSD or mild concussion are identified by the Institute of Medicine as substantially effective for soldiers and veterans. There is no gold standard, in fact, when we come to our clinical practice.

We have heard today that the scientific on CES data, the scientific data, while not perfect, does show significant evidence of effectiveness. In fact, top-tier academic psychiatrists prescribe the devices. They are widely used because they are effective and have been for decades. The research shows that there is a biological effectiveness in the increased levels of CSF serotonin and beta-endorphin as well as plasma levels and neurochemicals.

The cost and effort for conducting studies of effectiveness that meet the highest standards of scientific evidence are exorbitant and beyond the reach of these manufacturers. It is not surprising that none of them over the past 30 years have, in fact, conducted such large-scale studies. This was a device on the market, and particularly during the '70s and '80s, if you'll recall, during the '70s there was a certain negativity about electrophysiologic devices and certainly a negativity about research that was coming out of the former Soviet Union. So, I do not find it surprising that we don't have much larger and what we would now consider the highest level studies that validate the effectiveness of these treatments.

I do believe strongly that requiring the companies to conduct studies in accordance with the premarket approval would put them out of business and essentially deny care to soldiers and veterans. This is unacceptable.

CES is a practical treatment, as the patient can use the device in

the privacy of the home setting and, you've heard, in the combat arena and theater downrange; it does not require frequent or intense visits to a practitioner's office. CES is not costly, as compared to other treatments, either ECT, TMS, many medications, or alternative treatments, including interpersonal therapies.

The last slide.

CES is clearly low risk and effective in the treatment of anxiety, sleep disturbance, and depressed mood, especially with patients who abuse alcohol, prescribed medications, and illicit substances.

I prescribe CES for these co-occurring symptoms to patients with mood and anxiety disorders, including PTSD, sleep disorders, comorbid chronic pain, and alcohol and substance abuse, to patients who have not responded to psychotropic medications, dislike the side effects or are averse to drug therapy. They are carefully instructed on its use and to be alert for any changes that could be considered adverse. The patients are closely monitored by e-mail, telephone, and frequent appointments.

The military recognizes the benefit of CES in the treatment of soldiers and veterans. As you know, the Panel has a letter dated January 13th for reclassification from Colonel Hack, the Director of Combat Casualty Care Research Program at Fort Detrick.

I respectfully urge this Panel to reclassify CES for anxiety, depression, and insomnia in adults with drug and alcohol abuse. This

indication continues to allow for the treatment to reach many needy patients who may otherwise suffer for decades, especially our soldiers and veterans.

Thank you so much.

DR. HURST: Anyone else from Fisher Wallace?

MR. FISHER: No, no, we're all set.

DR. HURST: Thank you very much.

Then our next petitioner will be Neuro-Fitness.

DR. SMITH: My name is Ray Smith. I'm a physiological psychologist and I'm here to present, not for a specific CES device, but for CES in general. I have no financial interest in any CES company. I paid my own transportation because I live in D.C., and I think my hotel bill last night was paid by Neuro-Fitness. I certainly hope it was. I'll know soon.

As I look over the presenters here, I think I'm the only one of the presenters today who presented to the panel in 1977. I think the rest of us are all retired or gone somewhere fishing.

But, basically, the subjects I'm going to cover are summary of the studies, the site studies, summary of addiction studies, blood plasma and CSF studies, mechanism of action studies, follow-up studies, a look at the safety of CES, and then recommendations to the Panel.

And I'd encourage you, if you have questions or comments while I'm going on, to stop me and go ahead and do that while I'm talking to you.

As one of the other presenters noted, the Code of Federal Regulations, the law states what is valid scientific evidence to present to this Panel. And there's about four or five sections, but the first two are well-controlled investigations, which include double-blind studies, single-blind studies, and crossover studies, and the second one is studies and objective trials without matched controls, which are open clinical trials.

And I should state now that 95% of our studies in CES are psychological test studies, psychological tests, and it's a special form of science, if you will, a form of special training. Psychological tests and measures is a specific field, and I notice that Colonel Platoni is the only psychologist I've seen come before the Panel today. Those of you on the Panel who have psychiatric training, you will be familiar with tests and measures. Those of you in mental health work are familiar with psychological tests and measures.

The last thing I saw before I went to bed last night, unfortunately, was a summary some FDA person made, saying basically they had to go through all of our studies, and none of them science, and that we're terribly unsafe. And, of course, that ruined my night's sleep. But if you check back, that FDA anonymous reviewer is not trained in psychological tests and measures. He is not trained in behavioral science or statistics. He's no doubt a good statistician trained in some other area of statistics, but not in this kind of study.

And I'll go back to 1993. The first FDA speaker was saying in 1993, they were going to call the panel up, but FDA went through all of our studies and found out we had none, so they said what's the use of calling the panel? And they didn't. FDA allowed me to go through all of their library, and I checked to see what the problem was, and the problem is that the reviewer was an electrical engineer. He went through all of our psychological studies and discovered that not one of them is science.

So, I want to tell you, as a psychologist, what I'm going to talk to you today about, the double-blind studies, the single-blind studies, and so forth, are all psychological science.

By the way, I'm just summarizing the studies up to 19 -- 2008. I'm sorry. Some of other presenters, especially EPI, have submitted more additional studies later on. But up to 2008, there had been 18 depression studies in our literature. And these are all meta-analyses, and you have the data in your hands. The effect size averaged about 47%, right here.

FDA requires that we have at least two studies for you, the Panel, to say that we're effective in treating depression. We had to have two studies in which the treated patients got better than the controls. We're giving you 18. We're 16 ahead of what's the requirement.

And by the way, Prozac, which makes the drug scene -- and the FDA files what they submitted to the Panel. Their effect size was 5%, and yet they're the most hazardous prescribed medication on the market.

Insomnia. Our effect size was 60.

By the way, the yellow graphs are going from our standard area of the mean. If we did 18 more studies or 50 more studies or 100 more studies of depression, in 99% of the cases the effect size is going to fall between 30 and 62.

So, they said why don't you have more studies? We've been studying since 1963 in America. And when a psychiatrist asked me a couple years ago have you studied depression in the last five years, I said, well, yeah, we have, but it hasn't changed much since 1970.

The insomnia studies. Again, we've got 18 studies here that I'm reporting on today. We have more studies in the literature. The ones I'm documenting for you today, though, again, if we did another 18 studies and another 54 studies and we analyzed them 18 at a time, the effect size would fall between 40 and 83 99% of the time.

Anxiety studies. We've got 38 anxiety studies, well controlled.

By the way, these are all double and single blind, and we treated them in these studies below a sensation threshold. No patient feels any current, as EPI was telling you just a minute ago. Sometimes they put out devices where they'll have -- they preset the device so it doesn't pass current above sensation level and send out two groups of electrodes. One group passes current and one group doesn't.

Another way we've often done it in the past is through double-

blinding boxes. On double-blinding boxes there's a zero setting, and one, two, three, four. The therapist sets all patients on zero, plugs their device through the double-blinding box. On zero, all patients experience the sensation. They'll turn it up until they experience it, then turn it down until the sensation goes away.

At that point the therapist turns it down to a pre-randomized selected one, two, three or four. The therapist doesn't know which of those is treating and which is not. The patient doesn't know which is treating. He never sees the box. Actually, it's behind him. The physician or psychologist doing the rating of results is blind. And the psychometrist, the one doing the statistics, is also blind.

So, most of these studies we've got quadruple blind, if you will. We've got a blind therapist, a blind patient, a blind physician, and a blind statistician. So, they're very well-controlled studies.

Drug abstinence syndrome studies, the effect size running 60%. And, again, we did -- we've only got 16 studies. If we did another 50 studies, 99% of the time the effect size would go between about 42 and 78.

So, what I basically want to impress on the Committee is that, from someone trained in psychological studies and statistics, we've got all of the tests we need to show the effectiveness.

This is sort of it. I got tired of my regular graphs. This is treatment of cognitive function of CES, and the military has talked about

closed head injury studies, and we have studied closed head injury patients. What we've found is that we have functional problems over here, and these are addicts, closed head injury patients, ADHD patients, that kind of thing. And then we've got situational stress such as in pain patients and master's degree students in the University of Houston MBA program, for example.

The functional studies. What we found earlier on in -- I should digress a minute. When the NIMH sent me to the District of Columbia back in 1969 to head up their clinical research and training program, I had been taught and I was teaching people that every time you take a shot of alcohol, you lose thousands of brain cells and you don't get them back. Remember those days? No, none of you are that old. But the thing is we used to teach that's permanent damage, and what confused the whole world in alcoholism and drug addiction is, if we put the CES on the patients -- and these were hundreds of patients over time -- we put the electrodes on them for 45 minutes a day for 15 days, the brain damage came back to normal. They lost their brain damage.

We published that, and since then other addiction treatment centers have followed alcoholic patients over the years, and they have found that if they maintain sobriety for two years, the brain comes back to normal. So, it was not permanent damage. However, CES doesn't require two years. It does it in three weeks, over time and time again. The last time that was reported in the American *Journal of Clinical Psychiatry.*

There's a question at FDA about all of the studies that are done. They do like for us to study across -- not do them all in Charlotte, North Carolina, for example. We've got studies ranging from Harvard, Downstate Medical in New York. We've got UCLA San Francisco. We've got the University of Texas, San Antonio. We've got LSU medical school. We've got Mississippi State. We've got Tennessee medical school. We've got the University of Oklahoma.

All of these were either faculty studies, published studies, or they're Ph.D. or master's degree candidates done under faculty sponsorship. And so these are all what I would deem valid scientific evidence. Your FDA reviewer, if I understand what I saw in your file last night, dismisses all of these as being non-science.

I was going to do another one of these to show you all the other studies, non-university studies we've done, but it absolutely hid my whole map, you couldn't tell it was the United States, so I decided against it.

We've had studies done from -- okay, one of the things that we like to do when we study something like this, we like to see what is the placebo effect, because if you put a device on people's heads with electric current, you expect a placebo effect. There's going to be one. So, to do that, you have to design the study, which FDA does not require, by the way, you have to design the study so if you have 90 patients, you pre-test them all on whatever measure you're using -- and we're doing depression studies here.

These are four depressions studies. You pre-test them all, and then you put a third of them into active treatment, a third of them into sham treatment, and a third of them into wait-in-line controls. And the third group here controls for your placebo effect.

There's the same number here, the same percent here, because you're randomized into whose team won the Super Bowl, or lost it, if you will, and so forth. What we found is, with sham treated CES with CES electrodes on, we got this much placebo effect. That is not a significant amount in those four studies.

Again, I should say that the difference between CES treatment and these depression studies in this, on the medications that are out there, the difference between this and this is 1.8 scale points on the test. We're well beyond that.

These are five fibromyalgia studies done by EPI, and again, placebo control studies to see what they were like in pain patients. This is CES, and let's see, we're looking at depression again. This is CES and their depression score before they began. This is their depression score after 15 days of treatment. Here is the sham-treated group before, and here's the sham-treated group actually still depression. Here is the wait-in-line placebo controls. They started out depressed and they're still not -- so this basically is the placebo control effect. This difference between here and here is the placebo effect. There was no placebo effect. So, in the 10 studies or so that

we have in CES that actually controlled for placebo effect, we have never found it.

I'm going to show you, this is just a relationship. When we stress in pain patients here, as the depression is alleviated, the anxiety is alleviated, the pain is alleviated. Now, we're not treating pain. That's not one of our labels. But if you treat anxiety and stress in pain patients, the pain -- the sensation of pain goes down or is improved.

And you recall, after 9/11, psychiatrists all over New York City had an awful problem with the pain patients. Every pain patient they had went totally out of control after 9/11. And some of the devices sent to EPA, EPI might've sent devices in there to help control that. But because the anxiety went up, the pain went up. So, in pain patients, we always get improvement in pain because always get improvement in depression and anxiety.

This is improvement in cognitive function. Again, these are closed head injured patients. Some of them -- yeah, closed head injured patients. If we improve the depression, if we improve the anxiety, we improve the cognitive function. And, again, cognitive function is not one of our labels that FDA gives us. But as you improve -- and I'll show you an ADHD study. If the anxiety improves, the depression improves, the cognitive function improves. So, there's a stress-related cognitive function problem among patients.

Are there are any questions? Those are just the general studies. Are there any questions on those? I'm going to go briefly over the addiction studies again, which I'll be repeating.

This effect of treatment on keeping patients in addiction treatment. One of the problems in treating addicts is that they don't stay in treatment. They get very irrational. They're nervous, they're tense, they can't sleep, they can't stand the noise in the room next to them, and they leave patient treatment early. It's a very expensive cost when patients don't stay for full treatment.

This is Washington, D.C. in 1974. These are the patients leaving who didn't get CES treatment. These are the patients leaving against medical advice who did get CES treatment. So, there's a great saving.

The Dallas Comprehensive Care Corporation, back in the early 1980s, the Comprehensive Care Corporation had over 120 inpatient facilities across America. Again, they had an AMA rate. They had a 28-day program that costs thousands of dollars, and to lose AMA meant losing not a lot of patient treatment but a lot of money, if you will. The double-blind research in CES showed that CES patients dropped their AMA rates down to here.

This is London using -- this was over, by the way, a seven, eight-year follow-up. But this is London's rate of AMA, and this is what it was when they started using CES in the program.

This is Dr. Rosenthal's study in New York City, and he found the

treated patients with CES compared with those who weren't treated. He found those who weren't treated, their AMA rates is up here. Treating with CES brought their AMA rates down to here, a very significant change.

Here's Alabama. This was done with the EPI device, and it was reported in 2011. I think they did it earlier. But, again, these are court-appointed, court-referred addiction treatment patients. Their AMA rate was way up here. Alpha-Stim, in this case, brought it down, the CES treatment brought it down to here. So, the average improvement in addiction treatment is amazing, just by keeping the patients into the treatment program.

Here's the recidivism rate. And I want to bring this up again in terms of safety later. But the U.S. government survey said that treated addicts, over a six-year period, 40% of them come back for additional treatment. In Washington, D.C., we found that only 20% of them come back for additional treatment. In Dallas, the Comp Care study, they found only 20%. In London, over 8 years, they found less than 20% came back for treatment.

And, again, when these came back for treatment, they had all been treated with CES. If there had been a safety problem out there, they'd have found it by then. It would've showed up when they came back or before they came back. But certainly when they got them in their hands again, if there'd been some strange thing going on from the CES, that would've

showed up.

I want again to go over the blood and CSF studies. These were done with the Fisher Wallace device. These were 20 minutes of CES in 15 normal controls. They pre-tested them, and then they post-tested the blood. The serotonin went up, the tryptophan came down, the cortisol came down, ACTH went up, and the beta-endorphins went up. Of course, you'll note that, you neurologists, tryptophan is a precursor to serotonin, so you expect it to go down.

About 18 months ago I was giving -- in Seoul, Korea, I was doing a clinical conference, and a professor from the medical school said what happens if we use CES and nothing happens? I said check for his precursors, make sure the precursors are there. CES cannot make endorphins if the precursors aren't there or, in this case, serotonin. And so he said great. In clinical conferences almost all clinicians say give me a list of precursors. And they're usually an over-the-counter thing.

This is a study that was referred to early. Again, these are 14 -- this is a different study, but 14 patients given 20 minutes of treatment; increased serotonin; increased endorphins; norepinephrine, a little bit; the cholinesterase increased. Then, this is a treatment center in the Midwest who has treated, by the way, over 30,000 patients with CES. They took -- let me see how many they've got here. I've got an *n* for you here on this. Well, okay, they had 14 normals, if you will, and the next group were depressed

patients, and they had 11 depression patients who had failed on every treatment they had in the clinic. And they did plasma studies, CSF studies, and again they got increases in serotonin. By the way, they gave them 14 20-minute treatments over two weeks and then retested them.

The improvement in serotonin is up here. Beta-endorphins actually drop. Norepinephrine came up. The cholinesterases go up. The yellow bar is the percent of patients who claimed they had significant improvement in the depression or complete elimination of -- resolution of depression.

Here they have 23 pain patients, again, who had failed on every pain treatment program they had in the clinic. They pre-tested them and then post-tested them after two weeks, 20 minutes a day for two weeks. Again, the serotonin did not go up in these patients. The endorphins did. The norepinephrine and the cholinesterases went up a bit, but not significantly.

At the end of the study they had this many patients who were saying their pain had improved significantly or they were totally pain free. And, again, these are patients who failed on every pain treatment and every depression treatment that particular facility had to offer.

Are there any questions about those addiction studies? I'm going to get into the mechanisms of action, if you will. Some of these have been referred to briefly.

Dr. Pozos, at the medical school in the University of Tennessee,

he was doing basically an inferential study. He wasn't doing blood tests at that time, and he was studying dogs, and what he did, he was looking at adrenergic versus cholinergic systems, the balance in the brain that these two had to have.

So, he gave one group of dogs reserpine to blunt the reuptake of dopamine, if you will, and they looked normal still. Now, I've got to tell you, these are not normal dogs. If you brought the reuptake, then you can't recharge the presynaptic vesicles in a normal manner, but they're still normal.

If they gave them reserpine plus CES, the idea was if CES stimulates the neurons to release dopamine, then what's going to happen is the MAO is going to knock them out and you're going to end up giving the cholinergic response superiority over this. And sure enough, he found that when he used CES plus, he got Parkinsonized dogs. He took this group of CES patients -- he has patients who are now Parkinsonized, and he gave one group of them atropine to block the cholinergic response and he got normal dogs. He gave the other group physostigmine to increase the cholinergic response, and he got the worse Parkinsonizing of any of the dog preparations.

You know, here he takes these Parkinsonized dogs, he removes the reserpine. That's going to allow the axon to go ahead and start making normal amounts, if you will, of dopamine.

If you put one group -- he defined three groups. One group got

normal food and water. In three to five days, they came back to normal. They lost the Parkinsonized symptoms. One group got L-dopa. They were normal in three to seven hours. A third group got just CES, and they were also like this group, normal in three to seven hours. In his inferential studies, he's inferring that CES actually stimulated the increased manufacture of dopamine.

This is again morphine studies. Some were reported on earlier. This is the University of Texas at San Antonio -- at Houston. I'm sorry. Yeah, Houston medical school. These had morphine-addicted rats. He removed the morphine and he got, of course, abstinence syndrome. With the other group, he gave the other group CES, and again, in a time-dependent manner, they came back to normal. And he's saying that that shows they're generating endorphins again, where the morphine had down-regulated endorphin.

And, again, he used a similar group, morphine patients, where they'd been -- the endorphins had been down-regulated. He gives them naloxone to block the morphine, and it immediately produces the abstinence syndrome. If he treats with CES in a time-dependent manner, they do not show abstinence syndrome. They come back to normal.

So, he's inferring in both of these studies that CES is encouraging and increasing the brain's manufacture of endorphins in this case.

This is a human study, and these are all heroin addicts. And

this is Dr. Gold up in Pennsylvania, who brought us the 1-800-COCAINE hotline a few years ago.

Methadone, as you know, substitutes in for heroin, basically, and both of them down-regulate the production of endorphins. He's looking at, theoretically -- he had five physicians, all blinded to the study. He removed the methadone, which precipitated the abstinence syndrome. This group he gave alpha-methyldopa, and they were symptom free, that is, they brought the abstinence syndrome. However, they had rebound depression because alpha-methyldopa had down-regulated something else, and then they had to treat the depression.

This group over here, half the group got CES. These were symptom free, and no further symptoms resulted. And he's suggesting that, basically, CES is up-regulating the endorphin system again and competing against the adrenergic system in this case. And, again, his physicians were all blinded to who was getting what treatment until after the study, in which they had a group of depressions and they knew exactly what that group got. By the way, then they had to treat that with CES.

We're looking at potentiation of anesthetics here, medications. This is a study done with fentanyl, and this again was 50 urologic patients undergoing major urological surgery. And what they did, they put them -- the anesthesiologist put them under normal anesthesia with three or four different medications. But half of them were CES electrodes without current.

The other half were CES electrodes and were actively treated. What they found is that if they were CES, it required 29% less fentanyl to keep them under anesthesia during the surgery.

The second group of studies were all one study. Again, these were 50 -- oh, I'm sorry -- 90 urological patients and 50 abdominal patients, and while they had them under, they either gave them 75% nitrous oxide, 63% nitrous oxide, or 50% nitrous oxide and CES or non-CES. These are sham treated with the nitrous oxide. These are CES treated. And, again, they found that CES required 37% less nitrous oxide to maintain the same pain response of the patients.

So, those are basically the mechanisms. Are there any questions about the mechanism studies so far?

DR. HURST: I'm going to ask everyone to just hold questions until our question session --

DR. SMITH: Okay.

DR. HURST: -- which will be a little bit later. Thank you.

DR. SMITH: No more questions.

These here are follow-up studies, and again, these refer to safety. Again, this is an EEG sleep study. Okay, these are EEG sleep studies. And, again, these are the ones that were reported earlier. These were done by EEGs. Here's CES-treated patients in blue, light blue. Here's the sham-treated patients. Their sleep time awake did not improve. CES improved the

bedtime sleep, if you will, Stage 1 and Stage 4 sleep, and also it was all improved in the treated patients but not in the controls. The patients reported feeling rested and relaxed upon their rising. It increased tremendously after CES treatment.

Here they are two years later, the same patients. Here's the ones who treated with CES. Here they are two years later. They're back again, and they still maintain that treatment effect.

The sham-treated people who didn't have an effect, here they are two years later. They're doing something about their sleep, but that's not laying there thinking and staring at the ceiling. They're probably taking some somnorific of some sort. But they're still not reaching the improvement of the treated patients.

And, again, these are EEG studies over eight hours. You neurologists who spent your day in training especially watching an EEG graph roll past while your 32, 34 electrodes are following and tracing a pattern, you know exactly what to look for under those tracings. If you see something abnormal, that's what you'll get in your practice, you'll get tracings that are abnormal, and somebody, some technician flags those for you.

And here, after two years, they're watching for eight hours. They're watching for Stage 1 sleep. They're watching for sleep pattern. They're watching for Stage 1 sleep pattern, Stage 4 sleep pattern. They're finding nothing to flag abnormal. If they had it, I can tell you, and you know

it, they'd have stopped the study and gone to publication immediately. Two years after treatment with CES, they had nothing abnormal in their EEG.

This is state anxiety. Again, these are 23 ADHD patients. These treated patients, their state anxiety improved that much; the trait anxiety improved that much; real depression improved that much. Here they are two years later. The state anxiety is still down. I'm sorry, 18 months later. The trait anxiety is still down, the depression is still down. They have had no further treatment.

We were told in 1963, over -- in America, don't do crossover studies with CES. To this date, people are trying it, and when we got negative studies is because somebody tried a crossover, and when they crossed over and stopped treatment, the treated patients kept the patient response. After two years, 18 months, these patients still have their patient response.

This was their IQ test on the same ADHD patients. Going into the study, their full-scale IQ was less than 105; coming out it's about 117. The normal student entering -- the normal IQ for a student entering public universities in America is 105, and they weren't up to that when they began. The normal IQ of a student entering graduate school and public universities is 115. So, in two weeks' time, three weeks' time, we took them from not even being college eligible to eligibility for graduate school, if you will. And we're going to follow them up.

And here they are 18 months later. The verbal IQ is still going

up. The performance IQ has come down a bit. The full-scale IQ is still a master's degree entrance level. And, again, with no further treatment.

Okay. So, I think I'll stop here. I think safety, there's been enough. Again, let me just say one thing. We talked about recidivism rates. These patients all came back for additional treatment, have had CES treatment. There's nothing unsafe showed up in them.

London did norm studies on patients who had been through CES treatment and patients who had not. And those patients staying in the program longer, if they'd had CES compared with the London norms -- over seven years, by the way -- is way up here, above 60%. The recidivism rates over that seven, eight years, compared with London norms, is way down here.

The interesting thing that no other presenters brought up today is that the patients alive after eight years, if they had been treated with CES, the death rate among the drug addicts in our London study began at normal. It's 12%. It reduced it in half, to 6.1%. And I would like to enlarge on that just a little bit.

Here's statistics in London versus Comp Care, if you will, a study done in Dallas, and this is a study in the *New England Journal of Psychiatry*. Here's the London group staying for treatment. Twenty-four thousand patients were treated by Comp Care. They got these increases in patients staying for full program. London got this decrease in recidivism.

Comp Care got this decrease in recidivism. London counted the patients alive. Comp Care did not. But if we can infer that when they treated 24,000 patients with CES, if they reduced the death rate in half in America, which, by the way, is higher than it is in London, but still, if we use it, they've saved 1400 patients with just this treatment.

I'll say, by the way, that -- reported by Dr. Rosenthal, from the New York Phoenix House study, they treated at least 99 patients with CES. If they followed them up for the next 5 to 10 years, they're going to discover that in that treatment they have saved at least 10 lives of their addicts. If it had been classification II instead of Class III research and it had been a core treatment program in the treatment -- by the way, all of these recidivism studies, they're still studies because it wasn't put in Class II when the FDA recommended it in 1977. We're still studying.

Phoenix House, the largest -- they replaced Comp Care, so it's the largest treatment program out there. They can't go core program because they're still researching. Because they're researching, they're saving much fewer lives. If they had been treating every patient in that program as a core program, that came through that research project, they would've saved on the average, inferentially, 58 lives.

DR. HURST: Let me just mention, you have 12 minutes from now.

DR. WORCHEL: That should be enough. Thank you very much.

I'm Dr. Jason Worchel. And as a disclosure, I have no financial interests in any CES company. My travel expenses were paid by Neuro-Fitness.

I'm a private psychiatrist. I'm currently employed as the medical director for the East Hawaii Community Mental Health Clinic System, the Adult Mental Health Division, Department of Health, State of Hawaii, but I'm talking today as a private psychiatrist, not on behalf of the state.

I wanted to just follow up and emphasize some of the comments by Dr. Rosenthal and Dr. Xenakis.

Why I was asked to be here, the issue for me was, every day, when I'm faced with patients who are presenting with anxiety, depression and anxiety, I have to make choices in terms of their treatment. If I had highly effective treatments with low side effect profiles, I wouldn't be here. Hopefully none of us would be here. But as it currently stands -- and many of you who are in the field and are practicing know our treatment efficacy, particularly for depression, is woefully inadequate.

There's an ongoing controversy that most of my patients are aware of with regards to efficacy of the antidepressants, particularly in mild and moderate depression. They're very much aware of the side effect profiles and often will come to me with the advertisements that they've heard by various attorney firms soliciting them to file lawsuits against people like me for prescribing those medications. So, if I had at my disposal highly effective treatments with low risk and a low side effect profile, I wouldn't be

here.

I also treat a number of patients who refuse medications. They either come with an inherent bias against big pharma, often concerned that I have conflicts of interest, and as a result, they often don't trust me and/or the medications which I'm going to prescribe for them.

I think you're well aware that 80% of the psychotropic medications are being prescribed by primary care physicians who have limited time with patients, limited expertise, and that these patients are primarily then afforded somatic treatments, often with minimal referral to psychological treatment.

So, I want to address, I think, the central question, not of efficacy, which you've heard a lot about today, but the issue, I think, before this Panel is the question of is there worsening of the condition being treated as a result of ineffective treatment?

I think in some ways this is almost an insult to those of us who are physicians because what do we do every day? We see a patient and we provide for them a recommendation for treatment, and then, if we're doing our job, we're monitoring our patients in an ongoing fashion to determine whether or not the treatments we've prescribed are effective and what potential side effects may also be emerging as well.

So, it's not as if I am going to prescribe or any of us are going to prescribe any treatments and then essentially say we're going to continue

with this treatment regardless of its being ineffective. All of us, I think, attempt to strive for efficacy and monitor those side effects. The problems, I think, occur when the medications that we're prescribing are not taken by our patients, and we know the adherence rate is miserable for the psychiatric medications for anxiety, insomnia, and depression, and the patients stop them and they often won't tell us that they've stopped them.

So, in essence, I think the question before this Panel is, if this is going to be a device prescribed by a licensed practitioner, it's not the issue that the device may be ineffective; our medications are ineffective. I mean, read the literature. It's out every single day. Or if they are effective, they have, you know, an unacceptable side effect burden.

But the issue is this: Are we going to monitor the patients? That's not the responsibility of the device. It's the responsibility of the clinician. And, of course, we monitor our patients, and if it's ineffective, we would change. We would add. We would in some cases, as we've heard, maybe use it as an adjunctive therapy, or we would move on to other therapies.

So, I think to raise this issue as a concern that perhaps this device would in some ways preclude the patients from receiving evidence-based treatments that are out there now, I don't think is valid. I don't see any clinician essentially staying with an ineffective therapy. Of course, our medications are ineffective, we know that, but we keep attempting to change

the medications, change their dosages, or provide some other type of intervention. So, I want to make sure that that point is well understood.

Furthermore, I think with regards to the treatments that are out there, there are populations for which medications are really not indicated. We have a number of patients who may come in, for example, young mothers with infants who can't sleep. They're real concerned about taking medications that may put them to sleep and then they would not be able to awake during the night and respond effectively to their child. They want something that doesn't have that kind of effect. Well, what else do we have? Not much.

When it comes to the treatment of pain, for example, in the primary care setting, as we've heard, many of these patients are anxious and depressed. What is the doctor to do? They're afraid to give them other medications that may further -- either increase their potential for abuse and/or lead to accidental overdose, and we see that all the time.

So, with regards to CES, I think the evidence is very clear, the preponderance of the evidence, that it appears to be effective and that the side effect risk profile for significant adverse effects is extremely low, and that if the intervention is not effective, it's incumbent upon the practitioner, then, as we do now with ineffective medications, to make the appropriate change to help our patients.

So, in any informed consent process, we will make a

recommendation. We will put forward to them, the best as we can, the current evidence for efficacy and risks and side effects, leave it up to the patient to make a decision, and then follow them and change our treatment if it's required.

So, I would encourage you to allow CES to be in Class II, hold us practitioners accountable for its appropriate use, without the unrealistic concern that it would be used regardless of its outcome.

And as mentioned before, I think research is critical. It needs to be ongoing. It needs to be more in depth. You know, I started using CES in an fMRI environment just to see if it was safe, and in fact it is, and I am surely looking forward to more studies with the appropriate protocols to determine what is the pathophysiology involved, if it is effective, where is it effective and how is it effective, keeping it in Class II, or, I mean, allowing it to be in Class II, or allow this kind of investigator-initiated research to proceed without obviously the expense and the difficulty of having it as a Class III device.

Thank you so much.

DR. HURST: Thank you.

I believe Dr. Eydelman would like to make a comment.

DR. EYDELMAN: To address a statement made earlier, I wanted to clarify that the FDA Executive Summary was not written by any one single individual. Rather, it was a work of a collaborative, multidisciplinary team

comprised of psychiatrists, neuropsychologists, epidemiologists, statisticians, and engineers.

That's all. Thank you.

DR. HURST: Thank you, Dr. Eydelman.

I'd like to thank the petitioners' representatives for their presentations.

Does anyone on the Panel have a brief clarifying question for any of the petitioners? Please remember that the Panel may also ask the petitioners questions during the Panel deliberations in the afternoon.

Yes, Mr. Mueller.

MR. MUELLER: Yes, David Mueller.

I had a question for FDA. I'm just trying to figure out what happened back in 1997. What was the new information that became available to FDA that was relevant to the possible reclassification of CES, from your presentation?

DR. EYDELMAN: I believe this time period is for the sponsors, for the three petitioners, and there is a Q and A for FDA, and there's also quite an extensive FDA presentation which will hopefully elucidate it after lunch.

MR. MUELLER: Sorry.

DR. HURST: Thank you. Any other questions from the Panel? Yes, Dr. Yang.

DR. YANG: Lynda Yang.

I have a question for the EPI representatives, and I think it was mentioned in Mr. Elder's talk. This is a question about safety and vertigo. So, in the video clip there was a statement about you let it go or you can turn it up until you're dizzy; is that right? And then you turn it back down. And then there's also a separate setting that you're supposed to use for an hour to treat the dizziness. Okay, I may have misunderstood. And I have a question to follow that.

DR. KIRSCH: No, as soon as you turn it down, the dizziness goes away immediately. And most people like that effect. However, in research you never are dizzy because we never turn it up enough to make you dizzy. In clinical practice we turn up the current very slowly until the person feels a slight vertigo, then immediately we turn it down, the vertigo is gone, and they sit that way for 20 minutes, roughly.

DR. YANG: Pardon me.

DR. KIRSCH: No hour treatment. I don't know where that came from.

DR. YANG: Okay, is it dizziness or vertigo? Because they're different.

DR. KIRSCH: I'm sorry, I don't know the difference.

DR. YANG: I mean, to my understanding, vertigo is when the room is spinning around you, whereas dizziness is a perceived -- and I'll ask

the psychiatrists on the Panel or the neurologists. They can help me out there. But as I understand, there is a difference between the two.

DR. KIRSCH: People experience different effects within that framework. Not everybody has the exact same effect that they report. The most common explanation is you feel a little bit like you're rocking on a boat. You're welcome to try one and see it for yourself. Once you turn it down, the dizziness is gone, that quick.

DR. YANG: Dr. Hurst, could I follow that with one more question?

DR. HURST: Sure.

DR. YANG: So, as far as overdose goes -- and it seems to me that there's -- that if you're dizzy and that goes on for a certain period of time, perhaps is that not an overdose?

DR. KIRSCH: I don't believe there's such a thing as overdose. We have people on it for 24/7 for as much as 16 years, that I know of, and they're fine. There are actually people who like the dizzy experience. I discourage that in every possible way. You know, there are people who take four pills when they're supposed to take one. I don't know how to control that sort of thing, but it won't hurt you. Just sooner or later, that battery is going to wear out and you're not dizzy anymore, if you insist on being dizzy. I have never heard of anyone who sat around dizzy for any period of time. It's never happened.

DR. HURST: Ms. Carras.

MS. CARRAS: This could be for Dr. Kirsch or any of the other manufacturers.

DR. KIRSCH: Okay.

MS. CARRAS: So, the heavy feeling, I was wondering if you could talk a little bit more about that.

DR. KIRSCH: I can. I cannot tell you why. I would love to know why. But when you hypnotize people, you tell them to feel hot and heavy and then light, looks and limp, that sort of thing. Colonel Platoni is an expert hypnotherapist. You don't know why people become heavy or light from hypnotherapy, do you? You tell people to do that.

When you use the Alpha-Stim, not the other CES devices, the Alpha-Stim, this effect occurs without -- the patient has no prior experience. They have no orientation to the therapy. You put it on their ears, you turn it up, most people feel light at the end of the treatment. Some people feel heavy. If they feel heavy, we suggest they continue the treatment until two minutes after they feel light. And that's in the literature.

DR. HURST: Any of the other petitioners want to address that?

DR. XENAKIS: Yes, this is Steve Xenakis.

Just specifically, the issue of dizziness and vertigo is not a particular effect, and it's not used in terms of the prescription guidance to the patient with the Fisher Wallace device. I think that is unique to the Alpha-

Stim and not to the other devices, if I can clarify that. And I don't know of any reports of it with the Fisher Wallace device.

DR. HURST: Thank you.

Dr. Kotagal.

DR. KOTAGAL: Thank you for the excellent presentations. I had a question about the insomnia, which we have lots of -- there were lots of presentations about the insomnia. So, what type of insomnia improves? Is it something we call psychophysiological or primary insomnia? Is it an insomnia, say, that might occur with a neurodegenerative disorder? Is it somebody with emphysema or congestive heart failure? What specific type of insomnia are we talking about?

DR. XENAKIS: Does this go on automatically?

DR. HURST: No, it doesn't.

DR. XENAKIS: Okay. That's a good question. You know, as you saw from the presentations, the population that this device is used mostly with or largely with are the young soldiers and veterans. And so in most instances, neither within the Department of Defense, our military hospitals, or within the VA system do we particularly go through that kind of extensive assessment to ascertain what the specific etiology is.

I mean, we're getting patients, many of whom, by the way, as you also heard, are treated within the primary care setting, but we're getting patients who are coming to us, who've been in the combat theater many

times, exposed to any number of IED blasts, had all of the stress of combat during the times of their, you know, deployments, have also had their disturbed sleep cycles. I mean you, as you probably know and can imagine --

DR. KOTAGAL: Sure.

DR. XENAKIS: -- what that is like.

DR. KOTAGAL: No, I agree, but I'm just trying to narrow it down because, you know, are we talking insomnia in the context of anxiety and PTSD, or are we talking about insomnia in general? Because, you know, 30% of the United States population has insomnia.

DR. XENAKIS: Well, that's what I'm trying to characterize.

DR. KOTAGAL: Yeah.

DR. XENAKIS: So, we're talking about insomnia in the context of patients with PTSD, mood lability, headaches, perhaps from IED, musculoskeletal aches and pains. That's the cluster of how they present clinically.

DR. KOTAGAL: So, that's solely what -- when we had these presentations this morning. The scope of insomnia, is it restricted to anxiety and post-traumatic stress disorder? Or is it broader? So, that's sort of what I'm getting at.

DR. XENAKIS: Well, you know, I don't think I'm -- I think we're missing each other. We're treating the patient here, not the diagnosis specifically, and we're treating patients who come in with all those problems.

They have some and in a varying degree they could have PTSD --

DR. KOTAGAL: Sure.

DR. XENAKIS: -- and/or they could have pain from musculoskeletal that's aggravated by anxiety or sleep disturbance and/or they could be, you know, abusing drugs and alcohol.

DR. KOTAGAL: No, I understand that completely. I'm just thinking if the device is approved, say, Class II for insomnia, then it really opens up the field for use in a variety of other indications. So, that's what I'm sort of trying to understand.

DR. XENAKIS: Well, I mean, it opens up the field, but then -- so that we as physicians would have to just hypothetically have to decide, do we prescribe it for obstructive sleep apnea?

DR. KOTAGAL: Okay.

DR. XENAKIS: You know, we would have to make, as we do routinely --

DR. KOTAGAL: Sure.

DR. XENAKIS: -- that kind of judgment of is this the right treatment for this particular patient that has these problems?

DR. KOTAGAL: Thanks.

DR. HURST: Any other petitioners want to address that?

DR. SMITH: Let me just have a word about sleep studies. On the EEG sleep studies that we just showed, the diagnosis was primary sleep

onset insomnia for at least two years.

DR. KOTAGAL: Correct.

DR. SMITH: Okay.

DR. KOTAGAL: And that was from 1973, an old study, post-doctoral dissertation by Weiss.

DR. SMITH: The University of Illinois.

DR. KOTAGAL: Yes, University of Illinois. In that study, five subjects, five controls. And I think the latency certainly got improved with the CES, and there's no doubt about that. But in the discussion, they mentioned that the anxiety index in the controls was a bit higher in those subjects. So, you know, it's quite possible that the controls were sleeping in the sleep lab. If they are more apprehensive, that could be part of the reason for the insomnia.

DR. SMITH: Yeah.

DR. KOTAGAL: Now, at this point in this day and age, polysomnography is not used for assessment of insomnia.

DR. SMITH: The EEG study -- if I may.

DR. KOTAGAL: EEG is not used anymore, according to the American Academy of Sleep Medicine, and there are people who just published in the *Journal of Clinical Sleep Medicine*, 2008, is the guidelines.

But, you know, the tools that are used for assessing insomnia are sleep questionnaires like the Pittsburgh Sleep Quality Index, the

actigraphy, because when sleep is measured in the artificial laboratory environment, there's anxiety, if you will. So, it could work either way. So, I think the tools to assess --

DR. SMITH: I think what the doctor was just saying, any time we find a patient who has stress from whatever reasons, he's going to have a sleep problem. And if he's got stress from whatever reason, he's going to have increased anxiety, and he's going to measurably have increased depression on psychological tests. If we treat stress, we're going to treat a sleep problem. But for the one that's specifically represented here, they were taken in a sleep clinic at the University of Illinois, which the patients had complained for at least two years of primary onset sleep insomnia.

DR. KOTAGAL: Thanks.

DR. HURST: Yeah, other petitioners want to address that same question before we move on?

DR. CHIACCHIERINI: Yeah, I'm Dr. Chiacchierini.

Again, I beg to differ with your assessment of how sleep studies are required for FDA. I've been involved with submissions of several sleep studies to the FDA over the last five or seven years, and every one of them required polysomnography and EEG determination of latency to persistent sleep. So, there is a suspicion about the subjective sleep onset latency within the Agency at least, and therefore the study that was done in 1973 is very consistent with what FDA would require today.

DR. KOTAGAL: I would beg to differ with you, sir. Let me submit to you this article by Schutte, S-c-h-u-t-t-e, Rodin and others, *Journal of Clinical Sleep Medicine*, 2008, volume 4, issue 5, page 487. I'm just reading verbatim.

"Instruments that are helpful in the evaluation and differential diagnosis of insomnia include self-administered questionnaires, at-home sleep logs, symptom checklists, psychological screening tests, and bed partner interviews. Polysomnography and multiple sleep latency testing are not indicated in the routine evaluation of chronic insomnia, including insomnia due to psychiatric or neuropsychiatric disorders." And this is a guideline that they mention. "Actigraphy is indicated as a method to characterize circadian rhythm patterns or sleep disturbances in individuals with insomnia, including insomnia with depression." And this is listed as an option.

So, I mean, I would agree with you that even the FDA doesn't have it right. If they're using sleep latency as a measure for insomnia in the sleep lab, I don't think that's accurate. I mean, I think actigraphy or, you know, in-home assessments are what's really needed. After all, insomnia is something that bothers the patient in the home environment.

DR. HURST: Dr. Earthman, you're addressing Dr. Kotagal's question, correct?

DR. EARTHMAN: Correct. Dr. Brian Earthman.

From a clinician standpoint on the response to your question about what types of insomnias are responding to CES treatments, as a psychiatrist, if you were classified into initial, middle, and terminal insomnia, I see response in all three of those categories. That's one way to look at it. Another is by specific disorder type, mood disorder versus anxiety disorder versus substance abuse disorder.

And from a mental health perspective, I have not seen a type of insomnia that did not respond to that. Obviously an obstructive sleep apnea type insomnia --

DR. KOTAGAL: Sure.

DR. EARTHMAN: -- this device isn't going to be as effective with that. But in looking at it in those two types of ways, I've definitely seen a response there. In addition, in extreme environments such as a combat zone, we're able to see it. So, it's not just mild insomnia.

DR. KOTAGAL: Sure.

DR. EARTHMAN: It's significant and severe.

DR. KOTAGAL: Yeah.

DR. EARTHMAN: Additionally, I think on the insomnia point, when you do a treatment, as soon as the treatment's done, you're alert and you're ready to go. That's why you want to do it right before sleep, as opposed to some of other therapeutic options, which will create windows of time, you know, from sleep medications, 8 to 10 hours sometimes, where you

really don't want to be doing significantly --

DR. KOTAGAL: Sure.

DR. EARTHMAN: -- intensive tasks such as operating tanks or helicopters or probably even driving.

DR. KOTAGAL: Thank you. I've been a sleep specialist for 30 years and -- sleep medicine, and I just wanted to submit to you that we should try to narrow down what type of insomnia. We're talking about insomnia in the context of depression or anxiety --

DR. EARTHMAN: Correct.

DR. KOTAGAL: -- and that's specifically what we're discussing today.

DR. EARTHMAN: No, the more information that we can get as future research happens will be wonderful.

Could I also address the dizziness question earlier, since I'm up here?

DR. HURST: Yeah, yeah.

DR. EARTHMAN: Okay. Your discussion about the vertigo and dizziness with the use of the treatment, as a clinician, when my patients don't understand instructions completely and they have it on too high and they do get dizzy, which is a pretty broad term -- I think it actually is a different experience for most people -- it's unpleasant. They turn it off, and then they don't use it until they come back to me and say, Doctor, that was unpleasant,

what do I do now?

So, I think the reality is, if that does happen where there is a dizziness response, they're going to stop, it's going to subside, and they're going to come ask me.

DR. HURST: Thank you.

Dr. Fessler, you had a question?

DR. FESSLER: Yes, I'm trying to understand some of the methodological issues in the research presented. If your technique of determining a stimulation level for a patient is for them to turn it up until they become symptomatic and then turn it down just below that, how do you achieve a double-blind study? And if your answer is, well, in that case you don't turn it up that high, then how do you choose a stimulation level and how do you know you're doing anything?

DR. KIRSCH: Starting at the end, how you know you're doing anything is the outcome of the study. However, I'll remind you that I said dosage equals time inversely proportional to current. So, for clinical treatment -- by the way, the dizziness is proof of the CNS effect, but we also have fMRI studies, EEG studies, all kinds of stuff.

So, when you turn it up, clinically, they have an effect. They like to feel that because then they know they're getting a good treatment. Clinically, you should evoke the placebo effect in everything you can possibly do to help a patient, including polypharmacy, substitute the device or

something.

But as far as research goes, we trip over the normal time of treatment to compensate for the low current. It's that simple. You don't feel it. I have an Alpha-Stim here. You can turn it on, put it on 100 µA. You will not feel it. Somebody else can do it on the -- excuse me -- on the Panel, right now, it won't hurt you, and they'll say, behind your back, you know, if it's on or not on. You won't feel it. Then when you turn it up, you'll feel it.

However, we don't turn it up, we lock it for research. This device right here has software built into it for research, so that we can lock the parameters. The doctor can't set that, the patient can't set that, the PI can't set that. Only we can set that. We have to open up the device to change the software. We have to lock it in.

So, whatever the research you want, we can lock those parameters for research, and it'll be a conducting or non-conducting treatment. The timer will count down. You'll see the device will look like it's active or it'll be active. You won't know. The only way you'll know is the serial number. It's as good as a so-called sugar pill. Yeah, placebo.

DR. HURST: Dr. Good.

DR. GOOD: Thank you.

After reading through a lot of material and hearing the presentations today, I'm still struggling a little bit with some of the mechanisms. We've heard about changes in serum and CSF serotonin levels,

norepinephrine, beta-endorphins, but I'm trying to look for some sort of a unified sort of a theory here for why this might be effective. And I'm not sure who to address this to. Perhaps Neuro-Fitness or any of the petitioners.

DR. HURST: Turn your mike on, please.

DR. SMITH: That's the button. Okay. Hansitia (ph.), you'll recall the late Hansitia, had a notion that we're under stress in America, if you will, because we're getting a flat situation in our neurotransmitters or changed relationships to each other that are normally in balance and they maintain their own internal balance in a normal situation. If we get in a flat situation, they change, and as soon as that situation is gone, they come back to normal on their own. They self-regulate.

He's saying, however, that if we get into a chronic stress situation that we can't escape -- and there's a lot of that, as you know. It could be a bad marriage, a bad worksite. It could be the traffic on the way to work in the morning. But he said if we get in a situation where we can't stop the stress, then the transmitters shift to a new balance. And so he's saying, what we're doing in CES, we're shifting that balance back to normal, and what shifts it depends on what needed to be shifted, what shifted out of balance.

So, in the pain patients we shift their endorphins, whereas in the depression patients we don't. That wasn't their problem. We shift the serotonin.

So, basically we're saying that whatever the brain's doing, when

we get to them with CES, our task with CES is to put the brain neurotransmitters back into their homeostatic balance, pre-stress. And that's why, two years later, they're still where they were when we treated them, and that's why we can't do crossover studies.

DR. HURST: Thank you.

Dr. Arria.

DR. XENAKIS: I just want to make --

DR. HURST: I'm sorry.

DR. XENAKIS: I'm sorry.

DR. HURST: Let's hold the question, then you can address the last question.

DR. XENAKIS: Okay.

DR. HURST: Yes, thank you.

DR. XENAKIS: I just want to quickly respond to that because -- this is Dr. Xenakis, for the public record. So, as a clinician, I've asked the same question, and I'd like to know that there's some rational basis for using a particular treatment. In fact, in both my review of the literature and -- and I'm not a researcher, so I say this with great humility and in speaking to who I think the experts are. I've been advised and do believe that it'd be hard to discern what would be a real mechanism of action and figuring out how to model it.

I find that understandable, in that now, many 20, 30 years later

after the introduction of a number of these psychopharmacological agents that came out in the 1980s and looking at what were the hypotheses of their mechanism of action, we're hearing such a vast difference of how they've worked.

So, I don't think we know. I think we see that there are changes in the brain. I think that those changes in the brain indicate to us that it's not a placebo, which is important, and that therefore we're seeing a therapeutic effect.

Thank you.

DR. HURST: Thank you.

Dr. Arria. Sorry.

DR. KIRSCH: Okay.

DR. HURST: Yes, go ahead.

DR. KIRSCH: Okay. All of you have our 2009 submission to the FDA, and on page 29 there is a brief version of a 529-page doctoral dissertation that addresses this issue, which shows EEG and low-resolution tomography studies of the brain. It's interesting how changes occur at specific brain frequencies and primarily, over everything else, we see an increase in alpha, which is why my product's called Alpha-Stim. Actually, I assumed that before I had this kind of data. But we did not give you the full 529-page doctoral dissertation. It is on my website. Here you have a synopsis of it, and if I remember correctly, 18 pages with a lot of nice color

brain charts that show you where and at what frequencies. We also have an fMRI study conducted at UCLA in the 2011 submission. So, this goes to mechanisms.

Thank you.

DR. HURST: Thank you.

Dr. Arria.

DR. ARRIA: We heard a lot today about the clinical experiences that are associated with the use of CES, and namely, there were a lot of -- there was a lot of discussion around a wide range of clinical symptoms and conditions that CES has been used for. But what I'm struggling with is, from the research studies, it appears that there is again a wide range of patient populations for which CES has been used for. But there doesn't appear to be a concordance between the clinical experiences, the clear and compelling research evidence that is required for effectiveness and the indication of anxiety, insomnia, and depression. It appears that those three words take on different meanings in the research evidence, in the clinical experiences, and in those words.

And I even heard today we're not talking about disorder, we're talking about symptoms, and we're talking about substance use populations that have those, and we're talking about fibromyalgia patients that might have those symptoms, and I'm really struggling with, is there -- my question is -- sorry for the longwinded preface. Is there concordance or consensus

among the petitioners for the indications in the patient populations for those conditions for which CES has clear and compelling effectiveness data, research data?

DR. EARTHMAN: I'll attempt to add some light to that, hopefully. Yes, the term anxiety, depression, and insomnia, those are very broad terms and encompass many different disorders. I think one thing to look at in the research is outcome measures, okay. When we're using standardized outcome measures, if I'm looking at a research study, for example, to measure the effectiveness of a treatment dysthymia, okay, I might use the same outcome measure as I would in a study where I'm looking at treating depression, okay, or --

DR. ARRIA: But for which studies, show clear and compelling evidence for which -- point to the research studies that have those definitions described and that there is clear and compelling evidence. I understand the problem.

DR. EARTHMAN: Yeah.

DR. ARRIA: I'm trying to get at the solution.

DR. EARTHMAN: If you're asking, is there a specific body of research directly at post-traumatic stress disorder or panic disorder with agoraphobia, there are studies in there.

Scott, do you have something?

MR. ELDER: Yes. Scott Elder with EPI.

The standard is reasonable assurance of safety and effectiveness. That's the statutory guideline, is reasonable assurance of safety and effectiveness, and that the FDA provided us with the insomnia, anxiety, and depression when they initially regulated CES back in the late '70s. So, that's been the standard that we've been provided over these past 30-plus years. And it is a broad term on each of those, but that is the standard that we were provided to work with. So, within that parameter, we've had different research that works within those three different indications.

DR. XENAKIS: If I may, Dr. Arria, to answer from the standpoint of Fisher Wallace, if I understand your question, there is a discordance or a disparity in the operational definitions of anxiety, depression, and sleep disturbance, in terms of how clinicians assess those problems and the respective research studies that have been used to validate the application of the device.

Having said that, and for the purposes of this particular petition, I believe that that is why the company has elected to speak specifically or address those studies for the symptoms of anxiety, depression, and sleep in the substance abuse population because that just, as a practical issue, is the body of research that they have available to them.

DR. SMITH: I'd like to address that. It's a very good question, by the way. When we do research, we have to measure the depression with

something, and there's all kinds of depression. For example, the SSRI and HDRS, they were all measured, the depression they measured was with the Hamilton rating depression scale, and that's how they defined depression, with the Hamilton scale.

When I first began researching CES back in '72, I looked to see what the pharmaceutical companies were using. They were using the profile mood state back then. So, I started using the profile mood state. I defined depression in my depression study as the score on the profile mood state depression subscale. I defined anxiety as a subscale on that same test on the anxiety scale and so forth.

Later on we developed -- we've used other scales. For example, we've used also the Hamilton, and that defined depression in that study. We've used the IPAT, the Institute for Personality and Ability Testing, their depression scale. That defined that group of depression for that study. We've used the State-Trait Anxiety Inventory, which is, you know, again, to define state anxiety and to define trait.

So, every study we've got, the depression, the sleep, whatever we've got is defined by how we measured it and how much of a problem it was is defined by the measure, what they scored on that measure.

DR. ARRIA: So, you wouldn't agree with the previous answer that the indication is really among people with substance abuse disorders?

DR. SMITH: No, most of our studies have not been substance

abuse studies. But if an inpatient -- for example, the Texas prison system, their psychiatric ward. They wanted to study anxiety and depression on that ward. So, here comes in the master's degree candidates tell the prisoners we're going to put electricity on your head. How about it? You know, that kind of thing.

But we defined depression in that study, in those inpatients, by the test that was used. And I don't have that information right here. You have it, by the way, but I don't. We defined anxiety in that prison population, on that psychiatric ward, not because of the prisoners. The psychiatrist said, well, they seemed depressed and we're going to put them in the study for depression. That's fine. We start with what the psychiatrist asks us to do, and then we start measuring with a specific instrument, and that instrument defines not only the type of depression but how much of it they had.

By the way, we don't go to the DSM-III. No physician, I've never seen one who will have a patient in his office who said, I'm kind of down, I can't sleep, I don't eat, I feel blue. He doesn't get on his shelf and look up the DSM-III to decide whether that patient's depressed or not. He gives them medication or CES. But when we study it, we define it with our study instrument.

DR. HURST: Thank you. Let me remind the petitioners' representatives to just state their name when they come up. Thank you.

DR. WORCHEL: Hi. Jason Worchel.

I'd like to just, you know, briefly comment on that. It is confusing because I think when we're used to the pharmaceuticals, we're looking for specific diagnoses for which there's an indication, and they can't talk about, you know, bipolar depression if they haven't received approval, you know, for that particular -- and the way these particular studies appear to have been conducted, primarily, they use the rating scales, whether it was the POMS or the HAM-D or the Zung or whatever, and then subsequently determine, based on those rating scales, whether or not there was a statistical improvement.

And I think in general practice, whether perhaps we should be making more specific diagnoses, depending on which version of the DSM is currently in place, I think most likely the clinicians themselves will make a diagnosis based upon the constellation of symptoms that the patient presents and they may not even use a rating scale to do that.

So, I think it is confusing, but I do think the preponderance of evidence that show improvement in the rating scales, whether or not that rating scale -- and they are used in a variety of different, for example, categories of depression which we treat every day, from dysthymia to psychotic depression or schizoaffective.

DR. HURST: Thank you.

Dr. Eydelman.

DR. EYDELMAN: I just wanted to clarify. Just like drugs, every

device that is legally on the market in the U.S. has a specific indication for use. All other use is considered off-label use.

DR. HURST: Thank you.

Go ahead and continue to address the question.

DR. KIRSCH: Yes, I will. I'm still Dr. Dan Kirsch.

On page 377 of the letters book we provided with you, on the cover as well, but on page 377, in the actual context of the full write-up of this report, there is a scientifically valid survey. And that's why I'm not pointing to the cover of the book, I'm pointing to the context. So, you can actually read the survey consisting of military and civilian surveys compared to WebMD survey.

I had mentioned that Likert and VAS scales have been validated in a well-constructed study in the *Journal of Clinical Epidemiology*, and this is actually a collapsed Likert scale that we used very conservative means to come up with the data. And it just says, you know, are you sleeping better? The WebMD question is "This medication has worked for me." It's a strange sentence construct, but that's what it is. And so this didn't qualify. I do believe it's better for sleep onset insomnia. However, this didn't qualify that. This just said, you know, are you sleeping better?

And so the results in Lunesta were 56% of the people who responded to the WebMD survey said that they're sleeping better; 68% on Sonata; 81% of the military service members said they're sleeping better on

Alpha-Stim, and 84% of the civilian population said they're sleeping better on Alpha-Stim. Ask a simple question, you get a simple answer, and that's what this data is.

And again I remind you, Mr. Elder just reminded you of the Code of Federal Regulations defined CES as the treatment of anxiety, depression, and insomnia. It doesn't say anything about any patient population and, you know, for us for 31 years, we have never limited it to any patient population. What for? It works across the board. There's no difference. Insomnia's ubiquitous in all patient populations.

Thank you.

DR. HURST: Thank you.

Dr. Yang, do you have another question?

DR. YANG: Following up on something that Dr. Good said, I'm going to address this to Fisher Wallace representatives. Dr. Kirsch --

DR. HURST: Excuse me.

DR. SMITH: I just wanted to say one more word about the discussion we're just having.

LT RUSSELL: I'm sorry, our question and answer period for that question is over. You will have additional time.

DR. SMITH: Okay. Is there another question up?

LT RUSSELL: Yeah, by Dr. Yang.

DR. HURST: Yes, there's a question being asked now. You'll

have an opportunity a little bit later.

DR. YANG: So, regarding the mechanism, there was a statement by Dr. Kirsch who had said that the dizziness is an effect or is evidence of CNS effect, but the Fisher Wallace device doesn't have that. Do you want to address that? Does that mean it's working by some other mechanism or does it not -- you know, are you worried about effectiveness at all?

DR. XENAKIS: This is Dr. Xenakis again.

What I tried to say before is that, in fact, I don't think we can discern what the mechanism of action is. I don't think that, necessarily, that means that it's not a suitable or reasonable treatment, because that's not uncommon in our medical practice, and I can't say that we know what the mechanism is, other than the eighth -- postulated eighth nerve effect.

DR. YANG: My question wasn't about that. It was about the statement that dizziness is a reflection of an effect on the CNS. And since your device doesn't have that, does that mean that it's different or is it working?

DR. XENAKIS: Does it work? We assert empirically that it works because, when patients use the device, they get a therapeutic benefit. And there are studies with that device that shows it has a therapeutic benefit.

Are there differences in the mechanism of action between the Alpha-Stim device and the Fisher Wallace device? I don't think we know that,

and I don't think we've done, particularly, the studies. We don't know if it's -- if there are similar therapeutic effects and there happen to be other side effects that are different is open to further study.

MR. FISHER: Chip Fisher, Fisher Wallace Labs.

You know, without making any direction comparisons, you know, just physiologically, the Alpha-Stim uses ear clips. Ours uses sponge applicators, dorsal, lateral, and prefrontal cortex. So, we have different methods of application. Ours is not an ear clip adaptor device. I'm not making any, you know, comparisons other than to tell you they're different.

So, we do not experience dizziness in our patients, and you know, we don't know why, but it doesn't occur. So, that's basically just there are physiological differences between the various devices.

DR. PAROS: My name is Dr. Lawrence Paros, and I'm President of Neuro-Fitness. And I know I haven't presented, but my petitioners have done so for me.

I just wanted to clarify one aspect about CES, and that is, as with the Fisher Wallace device, our device, the CES Ultra, does not have the same effects as EPI's device. There is no vertigo. The most the patient will experience is just a slight tingling sensation.

DR. HURST: Thank you.

Dr. Dorsey.

DR. DORSEY: First of all, thank you very much to the

petitioners for your presentations and the information you provided to us.

Building off the last question, do the parameters of administration of CES affect either the safety or efficacy of CES? Dr. Kirsch, for example, and his presentation on Slide 23, indicated that the current frequency is fixed. But on Slide 25, the studies that he cited, they vary in the duration of stimulation, the frequency of stimulation, and it seems like the location of administration also differs among the various petitioners.

DR. KIRSCH: I'm sorry, the location? Oh, where the electrodes go from the different devices?

DR. DORSEY: The other ones.

DR. KIRSCH: Correct, correct.

DR. DORSEY: And then for yours, it was the duration and frequency of stimulation. It seems to differ --

DR. KIRSCH: Correct.

DR. DORSEY: -- from the studies in Slide 25.

DR. KIRSCH: My Slide 25 is all Alpha-Stim studies. All I presented today was Alpha-Stim, period. Okay, I'm done with the '70s studies. I wasn't in the business in the '70s. I can't account for that. I was young. Still maybe in high school.

All right. So, these studies actually were pretty homogeneous in their protocols. The current might've been turned up a little higher. I believe the Kim study had a slightly higher current because he felt that was

necessary. I don't. But they wanted to get that done in 20 minutes, and I think that's the reason they did twice what we normally do in a study.

But, again, in that case it wasn't a problem because it was a single-blind study, and only the person got the treatment, and then the investigator came in and did the follow-up measures and took the blood pressure. So, the investigator was blinded to the conditions, which is normal protocol. So, no, it's pretty much the same.

DR. DORSEY: I'm not so much concerned about blinding right now, but if, for example, some of the procedures, Dr. Winick's study, the dose was the duration of the dental procedure.

DR. KIRSCH: Correct.

DR. DORSEY: Other cases, it was 20 minutes. Other cases, it was one hour. Some studies lasted 10 days. Some lasted one day. Some lasted three weeks.

DR. KIRSCH: Yes.

DR. DORSEY: Does that affect safety and efficacy of your device?

DR. KIRSCH: No. One treatment, most people, not everyone, will get an effect for anxiety. Depression takes about three weeks to get to a therapeutic significant level. For anxiety, one treatment will work, and we've shown you three out of what I believe -- we have seven studies demonstrating that with subjective and objective measures, and

psychometrics and objective measures. So, no, it's not safety or effectiveness. It just has to do with the length of the treatment.

We've also found that it takes about six weeks to change trait anxiety. You know, the chronic light checkers, personality trait or chronic anxiety, that differs a great deal from situational anxiety. So, yes, you can leave it on throughout the dental procedure.

There have been, I think, four studies in the old literature on other devices that are not even represented here, that used it intraoperatively, mainly with urological procedures, and decreased the need for anesthesia by one-third, for whatever reason. So, I don't think there's any safety or efficacy difference in how many treatments you have.

We've been on the market 31 years, and there are people who use it every day and, you know, they haven't had any adverse problems. I actually think it's better if you don't use it every day, clinically. Use it like every other day. But if you're having a panic attack or something like that, then you should use it. And this is consistent with pharmaceuticals as well.

DR. DORSEY: Do the other petitioners agree that the parameters of administration don't matter in terms of efficacy or safety?

DR. EARTHMAN: Real quickly from a clinical perspective. That's one of my jobs as I'm treating the patient, is to measure and monitor that. And people respond to treatments differently, and the research can't address, you know, particular lengths of treatments, particular numbers of

treatments, from a clinical standpoint. I'll reassess patients, as has been mentioned before, and modify treatment programs based on their clinical response, and everybody responds in a different way.

DR. XENAKIS: Steve Xenakis.

Could you please restate the question again, please?

DR. DORSEY: Sure. Do the parameters of administration of CES affect either its safety or efficacy? For example, the frequency of administration, the duration of administration, the location of the electrodes, the current used.

DR. XENAKIS: Oh, first from the safety perspective, the parameters in that -- the device maximally delivers 4 mA. It does not present any kind of risk in terms of safety. And the biomedical engineers, who have -- I've inquired, will tell you that it can almost be indefinite use at that particular power. The frequencies do not also make any difference, and there's a range in the frequencies so that there's no issue with safety when it comes to the range of those frequencies. In terms of the length of duration of treatment --

MR. ROMAN: There's a difference between frequency of use and frequency of the radio current.

DR. XENAKIS: Well, there are several frequencies here.

MR. ROMAN: This is Kelly Roman, with Fisher Wallace.

I think you're talking about frequency of use. We're talking

about -- Steve is talking about the radio frequencies that we employ, the patented frequencies. There's no safety issues with those. So, you could have 150,000 hertz, you could have 50 hertz; there's no danger there.

In terms of frequency of use, our labeling, we're specific about, you know, once or twice a day for 20 minutes each session. So, we and the doctors we work with limit the frequency of use to twice a day, each session 20 minutes. In most patients it's 20 minutes a day. And that's where we found optimal effectiveness, and it was certainly safe.

DR. XENAKIS: Yeah, I was going to say, the general way that the Fisher Wallace device is prescribed is first three days -- the device automatically turns off at 20 minutes. So, first three days, one session in the morning. For about 60 days, two sessions, no later than four, five o'clock because it does awaken the patient. You've seen the data about enhancement of cognitive performance; it may in some ways awaken the patient. And then after that they can use it two to five times a week, and there are patients who use it for years. And in that sense, as you said, it's a bi-temporal electrode.

So, when it comes to the effectiveness, each of these devices, at least in my review, appear to have comparable effectiveness, and we use it specifically with psychiatric. I use it with the soldiers and veterans who come in with this constellation of blast concussion problems, pain, and psychiatric problems.

DR. HURST: Thank you.

Dr. Anderson.

DR. ANDERSON: I noted in the training video, the patient training video, that it advises against driving while using the device. I'm wondering what the issue is with driving while using the device, and how soon after using the device is it safe to drive?

DR. KIRSCH: Dr. Kirsch again. I hope you enjoyed that video, and there's a half-hour version.

Basically, we err on the side of caution. People become very relaxed from the treatment and therefore can be distracted from driving. That's all there is to it. Once the treatment is over, I've never known anyone who couldn't function at the end of the treatment. But during the treatment, we actually encourage people to just relax, you know, during the treatment, if possible. It's not necessary. Some of our advertisements say use it while watching TV, working at your desk, that sort of thing. But because of dizziness, no tightrope walking. That would be a problem in case the current got turned up somehow. But driving is a potentially dangerous activity for someone who is undergoing a relaxation procedure. If you were doing progressive relaxation, you know, exercises, you wouldn't do those while you were driving, either. So, it's just a safety precaution.

DR. STEIER: A quick question. Ken Steier from New York City.

How much do the devices cost and who pays them? Do the

insurance companies cover it? Do other types of programs cover it, or is it out of pocket?

DR. KIRSCH: Okay. We have two devices. What does that one cost? The A. What? $795? $795 for an Alpha-Stim A. I don't have any clue what the other devices cost. You'll have to ask. And our other devices actually have two clearances, one for pain and one for CES. It's combined. We've had it on the market that way since 1981.

And that one is our new one. The Alpha-Stim M is $1,195. And it's $200 more in China. China's business grew 66% last year, and it's now 10% of our business.

However, as far as who's paying for it, we do have people who pay for it themselves. It's roughly 70%. I have the exact figures at home, but roughly 70% of private insured patients do get some reimbursement if their policy includes durable medical equipment. That's the biggest variable. And the physician fills out the statement of medical necessity and all of that. So, it depends on the policy, primarily. Our number one insurance reimbursement is from TRICARE. Right now TRICARE is our biggest customer in the United States. So, that's for active duty soldiers. We do a lot with them.

DR. STEIER: TRICARE covers the entire cost?

DR. KIRSCH: TRICARE covers the entire cost. However, it is -- full disclosure here. It is not an approved method of treatment. It is on a

case-by-case basis, but they're just paying.

And, frankly, not too long ago, a general in the Army, not the one present here, had a good experience with Alpha-Stim and he went to TRICARE and then TRICARE came to us and asked us for information. They have a copy of my book, *The Science Behind CES*, which the FDA also obviously has. They've referenced it. And it's an annotated bibliography. And they came to me for more -- okay, sorry. TRICARE is paying less. We give a discount to the government. I was just reminded. We support those who serve. We've also donated as much as we can to the military and to the VA.

So, as far as -- where was I? TRICARE. Oh, yeah, TRICARE asked us for information. And, in fact, last week I sent them the presentation I made here today because that's our latest, most concise scientific presentation, and that was the first time Captain Dosseri (ph.) replied to me on a first name basis. Thanks, Tom. So, we're now in dialogue with TRICARE, although they're paying.

MR. ROMAN: The Fisher Wallace device is $695 retail. We basically tell the patients and the doctors up front, that is not going to be covered. We say, in very few instances it's covered. This is something that patients pay for. We offer military, veteran soldiers and their families $495 as the retail. And we find that that price is affordable to most people. That's about it.

COURT REPORTER: Are you Kelly?

MR. ROMAN: Yeah, I'm Kelly Roman, Vice President, Fisher Wallace Labs.

DR. PAROS: Dr. Lawrence Paros from Neuro-Fitness.

I just wanted to inform you that our unit, the CES Ultra, is the lowest cost unit on the market, $350 retail. We generally give a major discount whenever there's a real dramatic need. I've given units away quite frequently. We generally do not approach anybody in terms of insurance coverage; the simple reason is that the ambiguous FDA's status for the unit, for the modality, precludes that possibility.

DR. HURST: Thank you.

Dr. Good.

DR. GOOD: Oh, I'm sorry. My colleague first.

DR. STEIN: So, I've heard several people refer to the fact that the military is using a lot of these devices, presumably, and just sort of focusing on the depression, anxiety, insomnia, and not on pain, any other things. Can anybody give me figures on how widely it's used? That's sort of the first part of the question.

And I've also heard reference to the fact that there's lots of people who've come back from Iraq and Afghanistan with anxiety and depression and post-traumatic stress disorder, and the Institute of Medicine has not endorsed the use of antidepressants, for example. But are there any military or VA guidelines, reports, consensus reports that have said that CES is

useful for any of these conditions? Because I'm not aware of any, so I'm just wondering if I just don't know about them.

DR. KIRSCH: Okay. I had mentioned before, we provided you with a letters book. However, I also encourage you to look at the letters that were marked "do not post." We got those through the Freedom of Information Act, except some people sent us letters. One of those people was a colonel, the co-chair of the PTSD task force for the U.S. Army, and we had that included in the standard of care in 2010. It was published under the pain guidelines. It left the final committee, like this one, for PTSD to be included as a standard of care.

When it was printed it wasn't that way and -- well, I'm just going to say, Colonel Lowry, you have a letter from Colonel Lowry, who you're welcome to call and discuss this with. He's pretty upset that the committee decided something and then whoever didn't print -- took it out in the printing.

In addition, we have provided you with information on usage in the military. And what you can do, if you're based here, is just go down the block to the National Intrepid Center of Excellence at Bethesda Naval Hospital, which is the PTSD and TBI center for tri-forces, for the military, on the grounds of the Bethesda Naval Hospital. It's the National Intrepid Center for Excellence, built and donated to the military by the Fisher Brothers. And that facility uses Alpha-Stim on every single soldier going through the facility.

That's 100%.

And understand, there's no way we can sell them on doing that. It has to work or they wouldn't do it. So, that's why I encourage you to read the letters.

But as you can see, the incidence has gone up. We don't even market to the military anymore. Because it's growing so fast on its own, we just let it grow. That's based on results.

DR. HURST: Thank you.

Dr. Good.

DR. GOOD: Yes, thank you very much. I wanted to thank EPI for letting us look at the Alpha-Stim, the stim device. By the way, thank you for passing it around to the Panel.

DR. KIRSCH: You're welcome.

DR. GOOD: And also thanks for the patient educational brochures that are in the package. I was reading through that, and there are a couple of statements in there that I hadn't -- that related to things I hadn't heard in the presentation. I don't want to take them out of context, but on page 8 it says the device is appropriate for emergency medical or military applications. I'm assuming that's more for combat situations, but I didn't hear about emergency medical applications.

And there's another comment -- it's in the brochure -- that "it's effective in 9 out of 10 people." And I wonder if you might comment on some

of those things.

DR. KIRSCH: The 9 out of 10 comes from a 1990 series that we did in conjunction with the PMA we filed back then, which is still pending, and that's why we don't want to do another PMA, because the FDA was just absolutely horrendous about that. We've documented that in our response. The FDA kindly allowed a 90-day letter period for this. Look at our response, 48 pages. It gives the history of our dealings with the FDA. There's a book being written about that right now, by the way, by a newspaper editor.

So, we did determine that 9 out of 10 people had a significant effect, which we define as 25% or more improvement on scientifically valid user surveys. We have upped that now to 29%. I'm sorry. Anything under 29% is excluded. Thirty percent. But in the '90s we were looking at 25% and up being -- that's how we derived the 9 out of 10. And that's from both practitioner and patient surveys.

So, as far as emergency use for panic attacks and that sort of thing, Colonel Platoni will address that.

DR. PLATONI: Thank you. Kathy Platoni.

In terms of combat situations in which any number of psychological emergencies might arise, we used it extensively to diminish hyperarousal symptoms, to diminish symptoms of panic, to improve sleep across the board when people were too exhausted for being out on mission and being unable to sleep for days on end consecutively, in order to get them

to sleep, in order to allow them to go back out on mission.

So, in essence, the use of CES in the combat theater, in my experience in both Iraq and Afghanistan, extensively, is that CES is a force multiplier. It allows soldiers to function without the benefit of medications that might impair them. And, again, there's that waiting period between taking the medication and going back out on mission, and sometimes you can't predict when you're going to come under attack. So, again, CES has been a force multiplier across the board in my experience.

Thank you.

DR. GOOD: Just a comment. I can understand -- Dr. Good again. I can understand in that situation, but the educational brochure, I believe, is for the civilian population. Would this be appropriate for emergency non-military applications as well?

DR. PLATONI: Absolutely, absolutely. And I have used it in my civilian practice. I don't have a large number of emergencies, but in order to help people diminish particularly symptoms of panic, yes, I would say yes.

Thank you.

DR. XENAKIS: This is Steve Xenakis.

I'd just like to answer Dr. Stein's question here about the military's endorsement, I think is the way -- and I know you probably have looked at a lot of the literature being collected by the Department of Defense. In fact, the guidance for the treatment of PTSD and IED blasts and

pain is very general and in line with people using best clinical judgment.

There are, as you saw, four studies being done within military settings. It is a rather protracted process. Before the military decides to publicly endorse or certify any particular treatment, it will go through several extensive studies because of all sorts of implications having to do of regulations as well as scrutiny by the public and by the Congress.

So, to me it's not surprising that we don't have a public endorsement in that way, other than the letter from Colonel Hack, which in his position, I think, really is a good statement and support for being able to make this device continuously available to our soldiers and veterans.

DR. HURST: Thank you.

I'm going to take our last question from Dr. Alexandrov.

DR. STEIN: Can I just respond to that? Is that okay?

DR. HURST: Yes. Sorry.

DR. STEIN: Yeah. I mean, the VA, there are clinical practice guidelines that have been developed by the VA and the DoD conjointly, and they have clinical practice guidelines that speak to the treatment of major depression and PTSD, and they're publicly available, and I just pulled them up on the website. I haven't gone through them in detail, but I know the PTSD ones pretty well, and as far as I know, they don't refer to the use of CES.

Now, you know, they have different standards and different procedures for listing effective treatments, but I just wondered whether

there was anything else out there that I didn't know about.

DR. KIRSCH: That's why I urge you to talk to Colonel Lowry, the co-chair of the PTSD task force. He will tell you that it was supposed to be in there and it's not in there, so we've got politics at play. And I don't know the reason. I think he does, but I don't. He will talk to you, I assure you. He was happy to talk to TRICARE about that, and he'll talk to you about that.

Just very, very quickly, since the last question was --

DR. HURST: We're going to move on to the next question now.

Dr. Alexandrov, why don't you just give us our last question.

DR. ALEXANDROV: Well, this is kind of tied in. It almost sounds like, from what you're describing, that the military is conducting an open-label effectiveness study, so to speak, and I'm just wondering what type of registry is going along with this, what sounds to be almost like endorsement of this particular product. And what type of safety endpoints are they following? For example, are they following worsening of the condition being treated as a result of ineffective treatment, since that would be one of the most concerning potential risks?

DR. XENAKIS: This is Steve Xenakis again.

I have met several times with both Colonel Hack and Colonel Castro, who are funding -- their offices from Fort Detrick are funding these studies. And since we are not directly involved -- and I will then defer to EPI, if they're involved -- that information is not -- they're keeping that

private and it's not been disclosed to us. And so I can't specifically say that I know that they are tracking those same criteria and issues.

I do want to just also clarify that the absence of identifying CES as a suitable treatment for PTSD in the DoD guidelines does not mean that it's not used and/or in fact endorsed by the clinicians. The process of something when it's publicly posted is a much more elaborate, as I said, and protracted process, and so you should not necessarily interpret that the absence of it being identified as an indication of either policy or position of the Department of Defense.

DR. HURST: Thank you.

We're going to move on to one last additional public comment by Dr. Diana Zuckerman, who will have five minutes for that presentation.

LT RUSSELL: I just want to add that Dr. Zuckerman, she had registered for the public hearing and the approximate time in which it was stated in the agenda, because the meeting was moving forward, so she came at that time, and so we are going to allow her to speak.

MS. FRANCE de BRAVO: I'm grateful. I'm actually not Dr. Zuckerman, but I'm presenting a joint statement for her with me, if that's okay. My name's Brandel France de Bravo.

UNIDENTIFIED SPEAKER: Do you have slides?

MS. FRANCE de BRAVO: I don't.

I'm pleased to have the -- thanks so much for accommodating

me, by the way. I'm pleased to have the opportunity to testify on behalf of the National Research Center for Women and Families.

DR. HURST: Excuse me. Do you have an affiliation that you'd like to tell us about?

MS. FRANCE de BRAVO: Yeah. I work at the National Research Center for Women and Families with Dr. Zuckerman.

Our center is dedicated to improving the health and safety of adults and children, and we do that by scrutinizing medical and scientific research to determine what is known and not known about specific treatments and prevention strategies. Our center has expertise in evaluating the safety and effectiveness of medical products and specifically treatments for depression.

In addition to my graduate degree in public health from Columbia University, I have some experience working with substance abuse and harm reduction and drug prevention programs.

Now, I'm here today to express our support for the FDA's position that the available scientific evidence does not support reclassifying cranial electrotherapy stimulators, or CES. The Class III designation for CES for the indications of insomnia, depression, or anxiety is warranted.

The studies that have been conducted on CES have conflicting results, with the more rigorous studies generally showing little or no advantage over placebo or sham. Overall, the studies are marred by small

sample sizes and inconsistencies that make them inappropriate to combine a meta-analysis or to compare.

Only 5 out of the 39 studies used DSM criteria to diagnose depression, anxiety, or insomnia, which is a major failure of these studies. The studies also failed to establish which patients with what kind of mental disorder or what kind of substance abuse are most likely to benefit and in what way. The studies also failed to establish the appropriate dose or even the appropriate placement of electrodes, as we discussed.

What the available evidence does establish is that in studies where there was a control group, the placebo was often as effective as the treatment. And the good news for those in the placebo arm is that they got some relief from their symptoms without any of the risks and without experiencing side effects like blurred vision, dizziness, headaches, or skin irritation.

Now, although having substantial benefits from placebo is not unusual in studies of depression, that's not a justification for considering CES effective. I'm particularly disturbed by the lack of rigor in the studies on adult substance abuse patients. As the FDA correctly points out, "There are differences in situational depression, anxiety, or insomnia related to chemical withdrawal versus these conditions as underlying clinical diagnoses."

Now, given the limited success of evidence-based substance abuse treatment and the high rate of relapse, the last thing substance abuse

patients need are devices that make promises they can't deliver on and which have risks that may outweigh the rare and rarely statistically significant benefits. And that would be a concern for patients with depression as well.

If a patient has already failed in attempting treatment with medication, it will contribute to feelings of hopelessness to also fail using CES, especially since most patients would consider electrical stimulation of the brain as possibly a more radical treatment.

Now, all of us share the desire to have more treatment options for patients, but the FDA is not supposed to allow snake oil on the market.

Now, today we've heard about brain cell regeneration, increased IQ, pain reduction, PTSD. It also treats insomnia, depression, anxiety, including trait anxiety. I think the only widespread health problem that it didn't seem to address today is obesity. So, I feel like maybe we should all be daily using CES. At least that's what I would have -- the petitioners would have us believe.

We do patients no favors by allowing the sale of medical products whose effectiveness is questionable, especially when more effective treatments are available, and even more problematic when the product has risks such as seizures, blurred vision, and adverse effects from electrical stimulation of the brain.

In conclusion, it's not possible to say that CES provides a meaningful improvement, compared to placebo, for insomnia, depression, or

anxiety. Perhaps some patients would benefit in some way, but the scientific evidence does not adequately define a clinically accepted target population for whom the benefits of CES outweigh the risks in the treatment of insomnia, depression, or anxiety. Since available valid scientific evidence does not demonstrate that CES is effective in treating those symptoms, any risks are unacceptable.

Under these circumstances, it would be unethical to clear CES for the market based on a 510(k) application with controls such as subjective reports from the physicians, who are paid for treatment, and to patients who are clearly vulnerable to placebo effects. What is needed is scientific evidence that CES is more effective than placebo and that the benefits outweigh the risks. A PMA is needed to establish whether or not that is true. Without solid scientific evidence, it's impossible to conclude that there's a reasonable assurance of effectiveness or the absence of unreasonable risk of illness or injury.

Thank you.

DR. HURST: Thank you.

Does anyone on the Panel have any questions regarding this last open public comment?

(No response.)

MS. FRANCE de BRAVO: Thank you.

DR. HURST: Are there any other additional speakers who would

like to make open public comments?

(No response.)

DR. HURST: Any questions for any of the other additional speakers for the petitioners?

(No response.)

DR. HURST: Okay, thank you.

At this time we're going to break for lunch. Panel members, please do not discuss the meeting topic during lunch amongst yourselves or with any member of the audience. We'll reconvene in this room at 45 minutes from now, which is going to be about 1:40. Please take any personal belongings with you at that time. The room will be secured by FDA staff during the lunch break. You will not be allowed back into the room until we've reconvened.

Thank you.

(Whereupon, at 12:55 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:46 p.m.)

DR. HURST: And at this time FDA will begin their presentation. Mr. Timothy Marjenin, you may begin your presentation.

MR. MARJENIN: Thank you, Dr. Hurst. Good afternoon once again, Panel members. I'm still Tim Marjenin.

The FDA staff members involved in the development of the proposed rule, the review of the petitions, and the FDA systematic review are shown here on this slide.

Following this introduction, I'll present some additional details about the device description. Next, Dr. Park will present a clinical background. Then Dr. Min will discuss FDA systematic review of the CES literature, and following Dr. Min's presentation I will present summary remarks.

The following description is based on the CES devices that FDA has evaluated and found to be substantially equivalent. This does not include investigational devices that may exceed or differ significantly from these characteristics.

The specific characteristics of the stimulation are somewhat variable. We have cleared CES devices that generate up to 4 mA. That 6 mA is incorrect. Simulation can also be monophasic or biphasic, using either a sine wave or a square wave, and there are several different frequencies for

stimulation that can be used, upwards of 500 Hz for the stimulation wave, with upwards of a 100 kHz wave as a carrier.

The electrode placement is also variable among the cleared devices. There are several configurations that have been cited in the various submissions, including on each ear lobe, behind each ear on the mastoid process, behind each ear and accompanied by one on the forehead, and on each temple.

It is important to note that, for using a particular CES device, the same settings and electrode placement can be used for each condition listed in the indications for use.

CES does not have a performance standard, and there is no CES-specific guidance document. And as I noted earlier this morning, the classification panel recommended that it was not possible to establish an adequate performance standard because the characteristics needed for effective stimulation were unknown, and as we will present later, this continues to be our position.

The characteristics I just discussed are based on substantial equivalence to the pre-amendments devices. They are not based on the results of clinical investigations. Due to the nature of the 510(k) process and the concept of substantial equivalence, clinical data would not be required to support a determination of substantial equivalence, provided that the characteristics of a new device are sufficiently similar to those of the

predicate.

And also as noted earlier, CES devices are indicated for treatment of insomnia, depression, or anxiety. This is the indication statement that FDA has found to be substantially equivalent in 510(k) submissions and is the subject of the petition from Electromedical Products International.

The other two petitions have proposed indications for use that FDA has not evaluated and found to be substantially equivalent in a marketing submission.

And so just as a point of clarification, Fisher Wallace has used as their proposed indications for use the "treatment of depression, anxiety, and insomnia in adult substance abuse patients who have failed to achieve satisfactory improvement from one prior antidepressant or sleep medication at or above the minimal effective dose and duration in the current episode, or are unable to tolerate such medication."

However, further on in their petition they also have -- they also stated two slightly different versions of this, involving populations that I believe -- sorry, Dr. Paros, I can't remember exactly what your indication was, but perhaps we could read that into the record later. All the indications are proposed for prescription use only.

FDA does not believe that the treatment of anxiety, depression, and insomnia in an adult substance abuse population can be considered the

same indication that is identified in the regulation, in other words insomnia, depression, and anxiety. And the Panel will be asked whether they believe this indication represents a different patient population.

And now I will turn the podium over to Dr. Park, who will present a clinical background.

DR. PARK: Good afternoon. My name is Larry Park, and I'm a psychiatric medical officer at FDA, and I'll present a clinical background for the discussion today.

CES devices have been cleared for the indications of depression, anxiety, and insomnia. In addition, petitioners have proposed additional indications of substance abuse-associated depression, anxiety, and insomnia.

It is important to note that these three conditions, depression, anxiety, and insomnia, are nonspecific terms, and they may refer to either a general mental state that is not necessarily representative of pathology, a symptom which is representative of a pathological state, or a diagnosis or pathological entity in and of itself.

In the FDA guidance document for industry, general specific intended use, different levels of specificity for indications for use are defined.

1. Identification of function
2. Identification of tissue types
3. Identification of organ system or specific organ

4. Identification of a particular disease entity or target population
5. Identification of an effect on clinical outcome

Focusing on the last two levels of specificity, which are the most important to CES devices, indications for use for medical devices provide identification of a particular disease entity or target population and identification of an effect on clinical outcome, for example, use of medical device improves the rate of durable complete remissions with chemotherapy.

Within these descriptions, it is implied that a specific disease entity or disorder is the target of the device intervention. For this reason, although depression, anxiety, and insomnia may refer to non-pathological states, symptoms of an underlying disorder, or the disorder itself, the current CES indications for use were examined as representative disorders, that is, major depressive disorder, generalized anxiety disorder, and primary insomnia, respectively.

Current psychiatric diagnosis is based on DSM-IV, the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition*. The DSM-IV has been designed to be an empirically based, standardized, and reproducible system.

Diagnostic categories are described in terms of specific criteria which consists of associated signs and symptoms. Utilizing this system, practitioners make diagnoses by engaging in a process of matching a group of

signs and symptoms experienced by the patient with those described for each disorder. While DSM-IV outlines multi-axial system with five different axes of diagnosis, we will focus on Axis I, clinical disorders.

This slide lists the general categories of Axis I disorders. We will discuss the categories highlighted in yellow: mood disorders, anxiety disorders, and sleep disorders.

Depression, as a symptomatic mood state, is most commonly associated with major depressive disorder, though it can be associated with other diagnoses. Major depressive disorder is the most common type of mood disorder, with major depressive episode being the essential feature of that disorder.

The criteria of a major depressive episode include a period of at least two weeks during which there's either depressed mood with the loss of interest or pleasure in nearly all activities. The individual must also experience at least four additional symptoms drawn from a list that includes changes in appetite or weight, sleep and psychomotor activity, decreased energy, feelings of worthlessness or guilt, difficulty thinking, concentrating, or making decisions, or recurrent thoughts of death or suicidal ideation, plans, or attempts.

Treatments for major depression include a variety of different classes of antidepressant medications, psychotherapy, namely, cognitive behavioral therapy, and device-based treatments.

Cleared or approved device-based treatments for depression include electroconvulsive therapy, cranial electrostimulation therapy, vagus nerve stimulation, and repetitive transcranial magnetic stimulation.

The risk of ineffective treatment of depression includes a potentially greater risk of suicide or suicide attempts, increased likelihood of hospitalization, and increased disability.

Anxiety disorders represent a phenomenologically heterogeneous and diagnostically divergent group of disorders which include generalized anxiety disorder, panic disorder with or without agoraphobia, phobias, obsessive-compulsive disorder, post-traumatic stress disorder, and acute stress disorder. Anxiety, as it is commonly thought of, is most often associated with the diagnosis of generalized anxiety disorder.

The term anxiety, like depression, is a symptomatic state and is characterized by nervousness, apprehensiveness, fearfulness, or worry. Anxiety serves as the cardinal symptom of generalized anxiety disorder.

According to DSM-IV, the essential feature of generalized anxiety disorder is excessive anxiety and worry, apprehensive expectation, occurring more days than not for a period of at least six months, about a number of events or activities. The individual finds it difficult to control the worry. The anxiety and worry are accompanied by at least three additional symptoms, including restlessness, being easily fatigued, difficulty concentrating, irritability, muscle tension, and disturbed sleep.

For generalized anxiety disorder, a variety of treatments have proven effective. Medications include benzodiazepines, buspirone, and some antidepressant medications. A number of psychotherapeutic modalities, including cognitive behavioral therapy and relaxation therapy, have also demonstrated long-term benefit. In terms of device-based treatment, the only devices cleared for anxiety are CES devices.

For anxiety, if inadequately treated, the typical course is chronic and may result in avoidance behavior to avoid situations that exacerbate symptoms. This may lead to increased disability. Furthermore, anxiety is often comorbid with other psychiatric disorders such as depression and substance abuse and may serve as a precipitating or causative factor of these disorders.

Like depression and anxiety, insomnia may denote a normally experienced non-pathological state, a symptom representing a pathological condition, or a disorder in and of itself. Generally speaking, acute episodes of insomnia of less than one month are not considered indicative of a disorder, while a chronic course lasting one month or more is representative of a pathological condition.

A distinction is also made between primary and secondary insomnia, with secondary insomnia arising as a result of an underlying condition and primary insomnia having no identifiable underlying cause.

The essential feature of primary insomnia is difficulty initiating

or maintaining sleep or non-restorative sleep that lasts for at least one month. The sleep disturbance or associated daytime fatigue causes clinically significant distress or impairment in social, occupational, or other important areas of functioning. An important aspect of the diagnosis of primary insomnia is that it is not due to any underlying mental disorder, substance abuse, or medical condition.

For primary insomnia, current treatments include the use of over-the-counter and prescription medications or dietary supplements such as melatonin or L-tryptophan. In addition, some behavioral and cognitive strategies have proven effective to improve sleep for some individuals. In terms of device-based treatments, only CES devices have been cleared for insomnia.

For inadequately treated chronic insomnia, ineffective treatment has been shown to lead to decreased quality of life and impaired daytime functioning, which can decrease productivity. Untreated insomnia is also associated with a significant medical comorbidity, such as cardiovascular, pulmonary, or gastrointestinal disorders, and psychiatric comorbidities such as depression and/or cognitive or memory disturbance.

Another category of disorders that have associated symptoms of depression, anxiety, and insomnia are substance-related disorders. These conditions are related to the taking of a drug of abuse, to the side effects of a medication, or to toxin exposure. Listed on this slide are common substances

of abuse.

The substance-related disorders are divided into two groups, substance use disorders, including substance dependence and substance abuse, and substance-induced disorders, which include substance intoxication and withdrawal.

The essential feature of substance abuse is a maladaptive pattern of substance use manifested by recurrent and significant adverse consequences related to the repeated use of substances.

Substance dependence is a cluster of cognitive, behavioral, and physiological symptoms indicating that the individual continues to use the substance despite significant substance-related problems. There is a pattern of a repeated self-administration that usually results in tolerance, withdrawal, and compulsive drug-taking behavior.

The essential feature of substance intoxication is the development of a reversible substance-specific syndrome due to the recent ingestion or exposure to a substance.

The essential feature of substance withdrawal is the development of a substance-specific maladaptive behavioral pattern with physiological and cognitive concomitants that is due to the cessation of or reduction in heavy and prolonged substance use.

While not considered core symptoms of substance-related disorders, depression, anxiety, and insomnia are common comorbid

symptoms. It has been estimated that up to 80% of patients seeking treatment for an alcohol-related disorder endure such psychiatric symptoms.

For depression, studies have estimated that 32% of those with alcohol dependence and 44% of those with substance dependence will have a lifetime diagnosis of major depressive disorder. Fifty to 67% of those with alcohol dependence will also report high levels of anxiety, while 30% of those with substance abuse will suffer from a lifetime anxiety disorder.

Greater than 60% of those with alcohol abuse or dependence will report insomnia problems, while those with substance abuse have a 5 to 10 times greater risk of suffering from a sleep disorder.

Treatment of substance-related disorders is determined by the specific substance of abuse and the specific disorder or pattern of use. Generally speaking, however, substance-related disorders are difficult to treat and demonstrate high recidivism rates. Few effective treatments exist to promote long-term abstinence. Intoxication states are often monitored and treated supportively. Active withdrawal states are treated according to the substance used.

Given that some withdrawal states are quite uncomfortable and may in fact be life threatening, for instance, alcohol withdrawal, tapering of the substance and support of treatment may be utilized. Longer-term abuse and dependence conditions generally do not respond well to pharmacotherapy, though psychotherapy or comprehensive psychosocial

psychiatric treatment programs may be effective in promoting long-term abstinence.

A distinction is often made between a treatment of the primary substance disorder and treatment of associated symptoms. In general, comorbid depression, anxiety, and insomnia may be treated symptomatically, if the severity and duration of symptoms warrants. In addition, care must be taken to avoid treatment with potential substances of abuse, for instance, opiates or benzodiazepines.

In addition to the risks of untreated primary depression, anxiety, or insomnia, these untreated symptoms, in the context of a substance-related disorder, may result in ineffective substance treatment, non-adherence to treatment, or relapse.

Now, I'd like to switch and say a word about measurement instruments. And I would add that we prepared this talk as a team, and as part of the team, Dr. Peter Como, who is an expert in neuropsychological measures, was part of the preparation. In addition, he's here in the audience if we have any specific questions regarding instrumentation.

As discussed above, anxiety and depression are subjective states that may be associated with an underlying psychiatric disorder. Because they are subjective states, no objective measures exist to assess their severity. Sleep or insomnia differs slightly from anxiety and depression in that it is a condition that is subjectively experienced, but also can be

assessed with externally measurable variables. Therefore, the gold standard assessment technique involves the application of appropriately developed scales and questionnaires that have been specifically designed to assess the severity of these states.

In order to ensure that these instruments are reliable and valid, they generally undergo testing to assess construct validity or answering the question if the scale is measuring what it claims to be measuring, and test-retest reliability or the reproducibility of results from a scale with repeated administrations and across assessors.

FDA accepts only scales with demonstrated validity and reliability as primary outcome measures for studies supporting product clearance or approval. Moreover, while many scales and measures have been tested and deemed valid and reliable, only certain instruments are typically accepted by FDA as primary outcome measures. For instance, valid and reliable externally rated measures are preferred as a primary outcome measure over unvalidated, unreliable self-report measures. Examples of accepted primary outcome measures will be discussed in the next slides.

The Hamilton Depression Rating Scale is a validated, externally rated measure used to assess the severity of depression symptoms. There are multiple versions of this instrument, but the basic rating scale consists of 17 items. This is the commonly used measure, and it's considered by many to be the gold standard with regard to assessment of depressive symptoms.

Another commonly used measure of depressive symptoms is the Montgomery-Asberg Depression Rating Scale. This instrument consists of 10 externally administered items and is intended to diagnose and gauge the severity of depressive symptoms. Some researchers consider it to be a more sensitive measure of change in symptoms associated with treatment.

The Hamilton Anxiety Rating Scale is a 14-item, externally administered measure that has been validated and is commonly used to assess the severity of anxiety symptoms. The items generally reflect the symptoms associated with generalized anxiety disorder.

Primary outcome measures for sleep or insomnia are objective measures based on externally observed findings. The most extensive investigation for sleep assessment is polysomnography, also known as a sleep study. From data collected from a polysomnography, different aspects of sleep can be calculated. These are some examples: latency to persistent sleep, total sleep time, and wake after sleep onset.

I would just note to the distinguished members of the Panel and the audience that there's a typo on this slide, and the Insomnia Severity Index should go below the next bullet, the questionnaires.

In addition, because insomnia can significantly influence one's subjective state, self-report questionnaires are often used to assess an individual's experience of sleep or next-day functioning. Measurements such as the Insomnia Severity Index, Pittsburgh Sleep Quality Index, and Epsworth

Sleepiness Scale may be used as secondary outcome measures to assess subjective states of insomnia.

Finally, a word about study design. There are basic study design elements that should be present in any study seeking to evaluate the effectiveness of CES, including but not limited to a randomized trial design to ensure comparability of the active treatment and control groups with respect to known and unknown confounders; a sham control group with successful masking to minimize any placebo effect; eligibility criteria based on a specific diagnosis; a clinically relevant measure of effectiveness; adequately powered sample size; use of appropriate statistical methods; predefined success criteria; and consideration for durability of effect.

This ends my presentation, and I'll now turn it over to Dr. Lauren Min.

DR. MIN: Good afternoon. My name is Lauren Min, and I am an epidemiologist in the Office of Surveillance and Biometrics, Division of Epidemiology. I will be presenting our findings from the systematic literature review on the safety and effectiveness of CES.

We will begin with a brief description of the background and methods for the systematic literature review, followed by a presentation of the main findings regarding the safety and effectiveness of CES for two indication categories: Category I, which includes treatment of depression, anxiety, or insomnia; and Category II, which includes treatment of depression,

anxiety, or insomnia in the substance abuse population. This will be followed by a discussion of the study design considerations of the papers included in this review and end with our conclusion.

Following receipt of the petitions, FDA conducted a new systematic literature review of CES for uses included in the FDA-cleared indications and in the subgroups of individuals with drug or alcohol-related issues. We sought to address the following questions.

- What is the evidence for effectiveness of CES devices for the treatment of depression, anxiety, or insomnia?
- What adverse events are associated with CES use for these indications?
- What is the evidence for effectiveness of CES for the treatment of depression, anxiety, or insomnia in the substance abuse population?
- And, lastly, what adverse events are associated with CES devices for these indications in the substance abuse population?

On September 14th, 2011, we searched MEDLINE, CINAHL, Web of Science, PsycINFO, and Embase databases using the search terms listed here. And our search of these five electronic databases was limited to journal articles that were published between January 1st of 1970 and September 14th, 2011.

We further limited our search to randomized controlled trials, observational studies, systematic literature reviews, and meta-analyses.

An initial search of the five electronic databases yielded 392 citations, which were reduced to 204 results when duplicate articles were removed. These results were cross-referenced with an annotated bibliography published by Daniel Kirsch, who is the founder of Electromedical Products International and developer of the Alpha-Stim CES device. Eighty-seven additional articles were identified in the Kirsch bibliography. This added to a total of 291 titles and abstracts which were screened for original studies, systematic reviews, and meta-analyses, which fit into either Category I or Category II indications.

In the screening process, 229 articles were excluded for reasons including non-approved use, non-journal article, non-systematic review, studies from the Kirsch bibliography that were published before 1970, non-human study, treatments not specific to CES, non-English articles, and not original research and case reports.

Full texts of the remaining 62 articles were examined by two independent reviewers for inclusion, of which 23 were excluded because either no data was presented or there was no clinical application. In the end, our systematic literature review included 39 articles.

For evaluation of Category I indications, we identified 32 studies examining CES for FDA-cleared uses of depression, anxiety, or

insomnia. There were 13 randomized trials, 17 observational studies, one meta-analysis, and one systematic literature review. These studies were published between 1970 and 2008, with 59% published during the 1970s.

Among the randomized controlled trials and observational studies, the sample size ranged from 8 to 197, with 80% of studies enrolling 50 participants are less. Study populations were heterogeneous, as some recruited inpatients from psychiatric facilities, to evaluate the impact of CES on a given pathological condition, while other studies recruited healthy volunteers to serve as their controls.

Depression was addressed in six randomized trials and six observational studies. Anxiety was addressed in 11 randomized trials, 11 observational studies, one meta-analysis, and one systematic literature review. Insomnia was addressed in eight RCTs, eight observational studies, and one meta-analysis.

It's important to note that many of these studies evaluated multiple indications.

Various assessment tools were used to evaluate measures of depression, anxiety, and insomnia. Listed here are some of the outcome measures used in the Category I studies. Some, but not all, of these measures are validated and appropriately applied assessment tools.

In the RCTs, a number of different CES devices were used, and some of the treatment attributes are presented here. As you can see, there

was considerable variability in the electrical parameters as well as in the frequency and duration of CES treatment sessions.

In the observational studies, there was also a wide range of CES devices that were used, and there was even greater variability both across and even within studies in the dosage, frequency, and duration of CES administration.

In our evaluation of the safety of CES, there were 10 studies reporting that no adverse events had occurred and 13 studies reported various adverse events. Some of the more common adverse events include blurred vision, headaches, dizziness, tingling on the forehead, and ineffective treatment. With the exception of ineffective treatment, the other common events resolved with the removal of the CES device.

More rare and severe adverse events were also reported in these studies, and these include one patient who had increased situational anxiety, worsening of depression symptoms in four patients -- and two of these patients required hospitalization for suicidal ideation -- two cases of new onset epileptic seizure, and one death.

It should be noted that these more serious adverse events cannot be directly attributed to the use of CES. And, overall, it is difficult to discuss the adverse events in terms of rates due to the small sample size and high attrition rates of these studies.

And, lastly, nine of the Category I studies did not report

whether or not any adverse event had occurred.

FDA has identified several potential risks of CES based on the literature. The Panel will be asked whether they believe this list is accurate.

- Worsening of the condition being treated as a result of ineffective treatment
- Potential adverse effects from electrical stimulation of the brain
- Potential risk of seizure
- Skin irritation
- Headaches
- Blurred vision

The Panel will also be asked whether the evidence demonstrates a reasonable assurance of safety for the indications for use of insomnia, depression, or anxiety.

We identified 12 studies evaluating the effectiveness of CES on measures of depression. Of the randomized controlled trials, one reported fewer depression symptoms in the active CES treatment group versus control, and in the remaining five RCTs, depression levels did not differ significantly between patients who were treated with CES compared to controls.

Of the observational studies that were reviewed, four reported improvement in depression symptoms after treatment with CES, and the other two observational studies reported no difference in depression levels

between the CES and control groups. However, there are methodological issues that make it difficult to interpret these results.

This table presents some of the key study design features in the Category I RCTs and observational studies evaluating depression. For each study listed here, we examined whether or not there was a control group; the presence of successful masking to minimize placebo effects; an a priori statement of the study hypothesis; if sample size was adequate using an arbitrary cutoff of 50; use of DSM diagnostic criteria to evaluate a specific indication; use of validated and appropriately applied outcome measures; determination of a pre-specified endpoint for success, and statistical adjustment for key confounders.

In this table an X indicates presence of the study design feature in a given study. Overall, it was evident that most of the depression studies lacked these important study design characteristics.

It should be noted that some of these studies showed positive results, while others did not. One study that reported a benefit of CES is a double-blind randomized trial published by Hearst and colleagues in 1974. In this trial, 79% of patients receiving CES reported being less depressed compared to a significantly lower 21% of patients receiving sham treatment. Despite these strong results in favor of CES, there was no pre-specified hypothesis. They enrolled 28 patients, four of whom were lost to follow-up. They did not use a DSM criteria or a validated and appropriately applied

outcome measure for depression, and there was no pre-specified endpoint for success.

One of the more well-designed studies that demonstrated lack of effectiveness for CES is a double-blind randomized trial by Passini. With 60 subjects enrolled, this study had one of the highest sample sizes of all the RCTs we reviewed. After two weeks of receiving the assigned treatment, depression levels decreased slightly in both CES and sham control groups, but this change was not statistically significant.

It is notable, however, that the magnitude of this decrease in depression was greater in the control group than in the active CES group, indicating a placebo effect. This study was also limited by the fact that they did not use a DSM diagnostic criteria or a validated and appropriately applied assessment tool for depression. In addition, a study hypothesis and criteria for success were not stated.

Of the depression studies included in our literature review, only two of the six RCTs had successful masking, and of the six observational studies, two had control groups and two studies had successful masking. Of the 12 depression studies overall, two studies had a sample size of greater than or equal to 50, one study used a DSM criteria, and one study performed statistical adjustment for potential confounders. None of the depression studies used validated and appropriately applied outcome measures or had pre-specified statements of the study hypothesis or endpoints for success.

There were 24 studies that investigated the effect of CES on anxiety. Of the randomized controlled trials, six reported a statistically significant benefit of CES treatment, compared to control, in reducing anxiety symptoms, while four trials demonstrated no difference in anxiety between these two groups. One RCT reported a reduction in anxiety at 15 days post-CES, but this effect was no longer significant at 26 days.

Of the observational studies, the majority reported a positive association between CES treatment and reduction in anxiety symptoms. In one single-arm observational study, improvements were reported for some, but not all, measures of anxiety, and two studies reported that CES did not have a significant effect on anxiety based on clinical assessment and standard inventories.

A meta-analysis of eight randomized controlled trials indicated that CES, compared to sham treatment, was associated with significantly improved anxiety. Similar findings were reported in a systematic literature review that examined 34 clinical studies. In this review, 77% of the studies reported decreased anxiety after treatment with CES, and the remaining 24% reported no benefit.

Category I studies of anxiety, however, also had notable limitations in study design. One of the more well-designed studies, however, is a double-blind RCT by Philip and colleagues. This study enrolled 21 psychiatric inpatients who had anxiety based on DSM criteria. After five days

of receiving the assigned treatment, anxiety levels were significantly reduced compared to baseline in the active CES group, but not in the control group. Although the pre- and post-anxiety levels differed only in the CES group, the authors did not test to see if anxiety levels were significantly different between the active treatment and sham control groups after receiving their assigned treatment, which is a standard statistical method in efficacy studies.

Other limitations in study design include lack of a pre-specified hypothesis, small sample size, and the absence of validated outcome measures as well as a pre-specified endpoint for success.

A double-blind randomized trial by Passini is an example of a study that did not demonstrate effectiveness of CES. As previously noted, this study enrolled 60 subjects, and after two weeks of receiving the assigned treatment, anxiety symptoms in both CES and sham groups decreased slightly, but this difference was not statistically significant. Notably, the magnitude of this decrease was greater in the control group than in the CES group for two of the three anxiety measures, again indicating a placebo effect.

Other methodological issues in this study include the fact that they did not state a hypothesis or criteria for success, and they did not use DSM diagnostic criteria or a validated and appropriately applied assessment tool for anxiety.

A summary of the study design limitations in anxiety studies are

presented here. Five of 11 RCTs had successful masking, and of the 11 observational studies, three had control groups and two had successful masking. Of all 24 anxiety studies, only three studies had a pre-specified hypothesis, four studies had a sample size greater than or equal to 50, five studies had a DSM diagnosis, two studies had validated and appropriately applied outcome measures, one study had a pre-specified endpoint for success, and one study performed statistical adjustment for confounders.

We evaluated 17 studies investigating the effectiveness of CES on insomnia. Of the randomized controlled trials, four reported statistically significant reductions in insomnia symptoms in the CES group compared to control, while the remaining four trials reported no difference between the two groups.

Of the observational studies, sleep improvement after CES was reported in four studies, while two studies reported no impact of CES on insomnia. One study reported improved measures of insomnia during the first week of CES, but these results were no longer significant at two weeks. And one observational study reported improvement in sleep latency in insomniacs, but not in subjects without a sleep disorder. In the meta-analysis, pooled results from two randomized controlled trials indicated no difference in sleeping disturbances between CES and control groups.

Most of the Category I insomnia studies lacked important features of good clinical study design. However, one of the more well-

designed studies is a double-blind randomized trial by Weiss. This study reported that the average latency to sleep onset decreased significantly, from 61 minutes at baseline to 11 minutes after CES in the active treatment group. In the sham group, average sleep latency remained nearly unchanged, from 61 minutes at baseline to 59 minutes after sham treatment. In this trial, masking was successfully carried out, and there was a specific hypothesis being tested.

However, inferences regarding a beneficial effect of CES was based on a sample size of 10 subjects. In addition, DSM criteria and validated outcome measures were not used, and there was no pre-specified endpoint for success.

An example of a study that failed to demonstrate a benefit of CES is a double-blind randomized trial by Hearst and colleagues. After five days of receiving the assigned treatment, active CES treatment and sham control groups did not differ in their anxiety levels. Although masking was successfully carried out in this study, sample size was small, with only 28 patients enrolled, there was no pre-specified hypothesis or endpoint for success, and they did not use DSM diagnostic criteria or a validated measure of depression.

Again, a summary of some of the methodological issues in the insomnia studies are presented here. Four of eight RCTs had successful masking, and of the eight observational studies, only two had control groups

and two had successful masking. Of all insomnia studies, only two had a pre-specified hypothesis, two studies had a sample size greater than or equal to 50, two studies used a DSM criteria, two studies used validated and appropriately applied outcome measures, one study had a pre-specified endpoint for success, and one study performed statistical adjustment for potential confounders.

FDA believes the available valid scientific evidence does not demonstrate that CES will provide a reasonable assurance of effectiveness for the indication of insomnia, depression, or anxiety.

The Panel will be asked to comment on the adequacy of the available scientific evidence in defining a clinically accepted target population for CES and the relationship between this population and the indications for use of insomnia, depression, or anxiety.

The Panel will also be asked whether they agree with FDA's conclusion that the scientific evidence does not support a reasonable assurance of effectiveness for the indications for use of insomnia, depression, or anxiety.

Studies in Category II discussed elements of drug or alcohol abuse and also addressed FDA-cleared uses of CES for depression, anxiety, or insomnia. We identified seven papers in our literature search, and all were randomized controlled trials. They were published between 1973 and 1995, with one-third of them being published during the 1970s. Sample size ranged

from 20 to 67 subjects, with 67% of the studies enrolling 50 participants or less. And the study population was, again, heterogeneous, particularly with respect to psychiatric characteristics.

Listed here are some of the outcome measures used to evaluate depression, anxiety, and insomnia in the Category II studies. It's notable that none of the outcome measures were validated and appropriately applied assessment tools. There was high variability in CES parameters, both across and within studies, as a number of different device types and electrical output characteristics were assessed, and CES administration also varied in dosage and frequency as well as in duration.

In our evaluation of the safety of CES in the substance abuse population, we found that none of the seven randomized trials reported whether or not any adverse events had occurred. We examined the effectiveness of CES separately in the alcohol use and the drug abuse or mixed addiction populations. Four papers examined the use of CES to treat depression, anxiety, or insomnia in subjects with alcohol-related mental health issues, and all studies described improvements in these indications in association with CES treatment. Similarly, all papers on drug abuse or mixed addiction populations also reported greater improvement in anxiety symptoms after treatment with CES.

However, Category II studies also lacked important features of good clinical study design. One of the studies showing a significant benefit of

CES is a double-blind RCT by Padjen that compares active CES versus sham control in 64 alcohol-dependent men. After four weeks of receiving the assigned treatment, the CES group reported significantly greater improvement in depression scores compared to the sham group. Although the main finding was positive, the study lacked a study hypothesis, a clearly defined endpoint for success, and validated outcome measures. Furthermore, both CES and sham control groups reported improvement in depression compared to baseline, which is suggestive of a placebo effect.

Of the seven Category II studies, only three had successful masking, two had a sample size greater than or equal to 50, one study had a pre-specified hypothesis, one used a DSM diagnostic criteria, one used validated and appropriately applied outcome measures, and none of the studies had a pre-specified endpoint for success or statistical adjustment for potential confounders.

None of the studies included in our literature review met all of the criteria for a high-quality clinical study that Dr. Park previously noted in his presentation.

In conclusion, the 39 papers included in our literature review reported inconsistent findings regarding the effectiveness of CES for treatment of depression, anxiety, or insomnia. However, due to key limitations in study design, the effectiveness of CES remains unclear. In the absence of demonstrated effectiveness, a key concern raised is that use of

CES in lieu of proven effective therapies may present undue risk to patients whose psychiatric conditions may worsen if left untreated.

This concludes my presentation on the systematic literature review of CES. Next, Mr. Marjenin will be delivering the concluding remarks.

MR. MARJENIN: I'll try to go through this as quickly and understandably as I possibly can.

First I would like to quickly review several parts of 21 C.F.R. 860, beginning with the definitions of Class II and Class III devices. According to the regulations, a device is in Class II if there is sufficient information to establish special controls that provide a reasonable assurance of safety and effectiveness. Being in Class II means that general controls alone are insufficient to provide this assurance and that special controls are needed. Examples of special controls include performance standards and guidance documents.

A device is in Class III, however, if there is not enough information to determine that special controls would provide a reasonable assurance of safety and effectiveness. The second part of the definition is that the device is life supporting or life sustaining, is for use which is of substantial importance in preventing impairment of human health, or presents a potential unreasonable risk of illness or injury.

Subsequent to our review of the 515(i) submissions and the available literature and in light of these definitions, FDA believed CES to be

Class III and that premarket approval is needed. I will go into more detail about this in the next few slides.

The petitioners have proposed several special controls for CES devices if they were to be down-classified, including limited postmarket surveillance, adequate instructions for use, compliance with voluntary consensus standards such as electrical safety, and that they would be available by prescription only. However, these proposed controls do not address variability in the device characteristics, especially with regards to the stimulation settings and electrode placement.

As I have noted earlier, this variability has been a significant issue regarding CES since the classification rule was originally published. The literature review presented by Dr. Min showed that there is variability not only within the settings themselves but also the treatment duration and the number of sessions.

FDA believes, therefore, that without addressing device characteristics, adequate special controls cannot be written based on the existing scientific evidence to provide a reasonable assurance of safety and effectiveness.

As I noted this morning, the original classification panels recommended that the effective settings were not known. Furthermore, the 1993 proposed rule cited a lack of evidence to support the effectiveness of one group of settings over another. Also FDA's new systematic review further

demonstrates a lack of knowledge about the critical stimulation parameters, effective ranges, and treatment frequency and duration.

The Panel will be asked the following question later on.

From there we can turn to the definition of safety. A reasonable assurance of safety is defined in 21 C.F.R. 860.7(d)(1): There is reasonable assurance that a device is safe when it can be determined, based on valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks.

The valid scientific evidence used to determine the safety and effectiveness of the device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use.

The two key points I would like to make here are that when using the device properly, the probable benefits to health should outweigh any probable risks, and that there should be an absence of unreasonable risk of illness or injury.

Adverse events have been inconsistently reported in the literature, as you have just heard, and 13 studies reported that adverse events did occur, most of which were not serious. Ten studies reported that no adverse events had occurred. However, 16 of the 39 studies did not

report, one way or another, whether any adverse events had occurred.

FDA believes that there may be potential for unreasonable risk of illness or injury because the condition may worsen due to ineffective CES treatment. As Dr. Park presented earlier, a worsening condition can manifest in several ways. There may be a greater risk of suicide, an increased likelihood of hospitalization, psychiatric and medical comorbidity, increased disability, avoidance behavior, and decreased quality of life and functionality.

As I will discuss in a few slides, the indications make few distinctions about the condition, and if a patient with a more serious condition were to be treated with an ineffective device, FDA believes there may be an unreasonable risk of illness or injury. FDA does not regulate the practice of medicine, and we understand that in clinical practice a clinician would make the judgment about whether to continue with treatment if it appears to be ineffective. However, we would also like to reiterate that the supporting data need to be provided before the device is allowed onto the market.

Next we come to the FDA definition of effectiveness, and I would just like to point out, is that when using the device properly, there should be clinically significant results in a significant portion of the target population.

The current indications as they stand, anxiety, depression, and insomnia, lack specificity and do not adequately define a target population

since they do not distinguish between treatment of symptoms versus the treatment of the underlying disorder, pediatric versus adult populations, monotherapy versus adjunctive therapy, and use as a first-line treatment versus use in refractory populations.

The indications that we have right now are in use due to their pre-amendments status, not as the result of their evaluation in a marketing submission. PMA review and approval would allow for specifying an appropriate target population that is supported by valid scientific evidence.

If CES were to be down-classified, the devices that have been cleared would not be required to make the distinctions I mentioned on the last slide. Furthermore, new devices would not be required to make those distinctions because they would be claiming equivalence to existing devices.

Also, as previously mentioned, none of the studies in our literature review include all of the essential study design elements that have been mentioned earlier. I would also like to point out that 60% of the studies, especially in Category I, were published in the 1970s. So, in other words, we have a lot of old data and not much has changed since then, although additional studies have been published.

FDA acknowledges that there have been numerous publications investigating the use of CES and that most have been positive. However, they all have significant limitations. Please note that the criteria that are listed on this slide were not used to further screen the 39 articles that were included in

the systematic review. Based on our review, as I just mentioned, none of the studies included all of these elements, and this makes it difficult to make any favorable interoperations of effectiveness results.

To quickly conclude, FDA believes that the available scientific evidence supports a Class III determination for the following reasons:

The available data do not support a reasonable assurance of safety and effectiveness due to limitations, as I have discussed. PMA review would allow for the collection of data on a defined population towards that effectiveness. Special controls proposed by the petitioners would not be sufficient to provide a reasonable assurance of safety and effectiveness because they don't address the variability of the device characteristics. And, third, FDA believes that adequate special controls cannot be written based on the existing evidence, and worsening of the condition due to ineffective treatment is a potentially unreasonable risk.

You will be asked the following question.

Thank you very much.

DR. HURST: I'd like to thank the FDA speakers for their presentations.

Does anyone on the Panel have a brief clarifying question for the FDA? Yes, Mr. Mueller.

MR. MUELLER: Yes, I'd like to follow up with the question I asked earlier. First of all, I have quite a few, but I'll start with the easy one.

In the first presentation this morning, you said, I think it was 1997, new information became available that caused changes in the FDA view. What was the new information?

MR. MARJENIN: So, following the final rule that classified CES as a Class III device and calling for PMAs -- excuse me, I'm just trying to quickly do two things at once -- we did receive a PMA from Electromedical Products, and based on some of the information -- I'm not sure of the exact information that may have been submitted either by EPI or other sources. But based on whatever information was received, as I mentioned, we believe that in order to allow the devices that were already on the market to remain in commercial distribution while we're potentially looking at reclassifying the device, it was necessary to revoke a call for PMAs. So, it's more of a process and procedure sort of thing, just so we could say, okay, you guys can stay on the market while we're taking a look at this information.

MR. MUELLER: And that was in '97?

MR. MARJENIN: Yes.

MR. MUELLER: Yes, just a quick second question, though, is we received during one of the handouts here, regarding -- sorry -- we received during one of the handouts here a statement that the blurred vision in the publications was when the electrodes were placed on the eyes. Is that the blurred vision that you were discussing in your presentation?

DR. MIN: Yes, that's correct.

MR. MUELLER: So, if the labeling said don't put it on your eyes, that would probably take care of that adverse event?

MR. MARJENIN: Well, that's not necessarily a labeling issue, I mean, depending on how the device was intended to be used. I mean, it's true that the devices that we've cleared do not use electrode placement over the eyes. However, because electrode placement over the eyes was in existence prior to 1976, it's conceivable that somebody could come in with a device comparing to a pre-amendments device that would use that type of electrode placement.

MR. MUELLER: Okay. So, special controls could be written that would cover -- to state don't put it on the eyes?

MR. MARJENIN: That's possible, yes.

MR. MUELLER: Okay. And then my last quick question is that the C.F.R. states valid scientific evidence -- and it was in our training -- includes well-controlled investigations, the gold standard, partially controlled studies without matched controls, well-documented case histories, and reports of significant human experience.

I noticed during the presentation that you threw out the case histories in your analysis. So, how many cases were thrown out and what were their effects?

MR. MARJENIN: Well, in terms of --

DR. EYDELMAN: Dr. Min will address this.

MR. MARJENIN: Well, in terms of the number of case reports, I think we have a number of -- the number for the case reports that were excluded.

DR. MIN: Eleven were excluded because they were case reports.

DR. HURST: Excuse me. Let me just remind everyone to say their name so that it goes on the transcript --

MR. MARJENIN: My apologies.

DR. HURST: -- before you answer or ask a question. Thank you.

MR. MARJENIN: So, if we could have the slide up, please. Thank you.

So, to your point -- and this is Tim Marjenin, by the way. So, as you've correctly stated, valid scientific evidence -- and it's a very big, long definition, so let's kind of whittle this down here. So, well-controlled investigations, partially controlled studies, and objective trials without matched controls, and so on and so on. So, that is the main definition for valid scientific evidence as it exists in the reg. However, based on the reasonable assurance of safety and a reasonable assurance of effectiveness, each part of those respective definitions include different levels of evidence.

So, for example, in a reasonable assurance of safety, Part (d)(2) says that among the types of evidence that may be required, when appropriate, to determine that there is reasonable assurance that a device is

safe are investigations using laboratory animals, investigations involving human subjects, and nonclinical investigations, including in vitro studies. So, for safety, that could include the entire body of evidence, as long as it fit the overall definition of valid scientific evidence.

MR. MUELLER: You also did not evaluate that. I remember you saying that you did not evaluate non-human studies, the animal studies.

MR. MARJENIN: We did not evaluate the non-human studies towards effectiveness. I don't know if Dr. Min wants to talk a little bit about the selection process.

DR. MIN: This is Lauren Min.

I can tell you that we excluded 22 animal studies from our literature review.

MR. MARJENIN: And so just if I can quickly move on to the definition for reasonable assurance of effectiveness. So, in Part (e)(2) of that definition: The valid scientific evidence used to determine the effectiveness of a device shall consist principally of well-controlled investigations, as defined in paragraph (f) of this section, essentially unless the Commissioner says otherwise.

And so paragraph (f) of that section states things such as provides adequate assurance that the subjects are suitable for the purposes of the study, provides diagnostic criteria of the condition to be treated or diagnosed, comparability between the groups, and there are a whole bunch

of other pieces of information, recognizing comparison groups and things of that nature.

MR. MUELLER: So, is one of them to state that you have to have a -- that the studies didn't have the pre-study acceptance criteria?

MR. MARJENIN: You mean predefined success criteria?

MR. MUELLER: Predefined success criteria. You had them in the ones listed.

MR. MARJENIN: I do not remember that off the top of my head.

DR. HURST: Mr. Marjenin, why don't you go ahead and answer, and then we're going to move on. I know a number of other Panel members have questions.

MR. MARJENIN: Okay. So, in terms of that specific one, there's nothing about predefined success criteria. But in reality, the major things that we were looking at was a randomized sham controlled study. Did they have a specific recognized diagnosis that they were studying, and were they using a clinically relevant measure of success? And just based on those several important criteria, none of the studies met all of those.

DR. HURST: Thank you.

Ms. Carras.

MS. CARRAS: Michelle Carras.

Dr. Min, you mentioned, under the risks, that there was a death

and two seizures, and our material discusses that there was a death three months after CES treatment, but there's no mention of seizures. I was wondering if you could elaborate on that.

DR. MIN: Sure. This is Lauren Min.

The seizures occurred in a paper by Philip, and I can tell you that this was a study of psychiatric inpatients with major depressive disorder, and in this study two patients had new onset epileptic seizures during a five-day washout period that occurred prior to CES treatment. So, this is a case where it's like the seizures are likely not attributed to the CES device, but we reported it here simply because we were reporting all of the adverse events that occurred in the studies.

DR. HURST: Dr. Steier.

DR. STEIER: Ken Steier from New York.

My question is for the panel. The devices have been used for approximately 30 years. There were, for instance, over 8.5 million treatments administered between 2007 and 2011. They're also used worldwide, even without a prescription. Over that immense period of time, if there was truly a safety issue, isn't it likely that that would be very obvious and we wouldn't have to concern ourselves with potential issues or problems?

MR. MARJENIN: I'm sorry, you said that was a question for the Panel or was that a question for us?

DR. STEIER: For you guys.

DR. EYDELMAN: Okay.

DR. STEIER: That small panel up there. Any one of you.

DR. EYDELMAN: I'll take this. When we evaluate information, we base it on the valid scientific evidence. So, having said that, we'll look at published literature as well as we will look at the official MDR reports. Unfortunately, if there's a wide use and not a well-documented body of information, that does not help us.

DR. HURST: Dr. Good.

DR. GOOD: So, a follow-up on that to make sure I understand. The MDR reports are the ones that report complications reported to the FDA; is that right? So, if I remember correctly, the petitioners said there are a very small number. I can't remember what it was, but it's less than 20 or something like that, that had been reported in association with this device. Maybe my figure is slightly wrong, and I'm sorry if I do. But I was wondering if the FDA would've taken it into consideration in their safety analysis.

DR. EYDELMAN: Yes, we actually looked at all available sources of information to assess the safety profile of these devices.

DR. HURST: Ms. Carras.

MS. CARRAS: It's Michelle Carras.

I was wondering if you could give us an example of some of the MDR reports that have come in about CES.

MR. HOFFMANN: This is Michael Hoffmann.

The number was correct. I believe it was three, what was quoted in the petitioner's presentation. And -- I'm trying to recall -- the uses for the device were off label. So, it was the device being used, but it wasn't for the on-label indications. And there were only three.

DR. HURST: Dr. Steier.

DR. STEIER: Dr. Steier again, from New York.

I understand that the FDA might not use that information, but us as experts and panelists being out in clinical practice, if I see a product that's been used for a long period of time in all types of patients all over the world and there's not any huge safety outcry, unlike other medications, for instance, that have been pulled from the market and things like that, I would wonder what's the real safety issue.

DR. EYDELMAN: So, we obviously value the input that we receive, hence the Panel meeting today.

DR. HURST: Dr. Anderson.

DR. ANDERSON: I have a question for Dr. Min. On your review of the literature on the treatment studies, were you able to determine whether the subjects in the studies, in particular the randomized controlled studies, were on concomitant psychiatric medication, and was there a difference between the treatment group and the control group in terms of medication usage?

DR. MIN: This is Lauren Min.

Some of the studies, particularly the ones that looked at psychiatric inpatient populations, they did. Some of them had a washout period where they took them off their medications. Other studies used CES as adjunctive therapy. They did not perform any subgroup analyses to give you that answer.

DR. HURST: Mr. Mueller.

MR. MUELLER: Dave Mueller.

You mentioned in your presentation the different settings that were used, and there was a large range of parameters and settings on the device. However, if you were to group the settings, were they all below the 4? I believe it was milliamps.

MR. MARJENIN: And this is Tim Marjenin.

If you were looking specifically at current amplitude, then, yeah, the studies that were included in our systematic review, they were below the 4 mA that we have cleared.

MR. MUELLER: And then the frequency, not as in electrical frequency, you were talking more about times per day, that was your point?

MR. MARJENIN: Well, there's also the frequency, the electrical frequency of the stimulation itself, and there is the number of treatment sessions. Those are two different things.

MR. MUELLER: Right. And so with the electrical frequency, could they be grouped within a range of X to Y?

MR. MARJENIN: There are several specific frequencies, treatment frequencies, not including the carrier frequencies that have been cleared. It may be possible to group some of them based on that, just because we have really only seen specific frequencies instead of being able to adjust it over a continuous range.

MR. MUELLER: All right, thank you.

DR. HURST: Ms. Carras.

MS. CARRAS: It's Michelle Carras.

I have a question also about regulating specific dosages and frequencies. I understand that in some cases like with ECT, the guidelines are left up to the practitioner. So, I'm not clear how FDA goes about assessing how to determine whether the guidelines are left up to the practitioner or it's necessary to have that be part of the classification.

DR. EYDELMAN: So, each device and its approval range will usually indicate the specifications for its approval. Sometimes it's a range and sometimes a very specific output, so depending on the device in question.

DR. HURST: Dr. Arria.

DR. ARRIA: Amelia Arria.

I'd just like to ask Dr. Min, in the review of the literature, whether she could clarify something about the general timing of the administration of the device and when the outcomes were measured. I know

that you can't do it for every study, but I'm stilling trying to get a sense of the quality of the studies and how many of them varied on that. You understand what I'm talking about?

DR. MIN: This is Lauren Min.

The follow-up duration varied. If I recall, there's one study that there was a single treatment session, but most of the studies, the treatments occurred from two weeks all the way to several months. But even among those studies, how many times patients received the CES treatment sessions, it differed. For some studies it was once a day, for other studies it was twice a day, and in several of the studies they had the subjects take the CES devices home. So, in that case adherence -- there's an issue of adherence. We have no idea what frequency or duration of the CES treatment those patients actually received.

DR. ARRIA: And what is that in relation to when the outcome was measured? Like, did they stop the treatment and then measure the outcome or was it measured right after or --

DR. MIN: In most of the studies, the outcome was measured on the day of the last CES treatment. Yes.

DR. HURST: Dr. Good.

DR. GOOD: So, the petitioners gave us quite a bit of information this morning that included sham treatments, included some fairly long-term outcome information, and I'm assuming that the information that

they presented would've been among the studies that you discarded because of a lack of scientific quality; is that correct?

DR. MIN: I'm sorry, I don't recall exactly which references they included.

DR. GOOD: Well, I think all of it. But we saw a number of graphic descriptions here, especially bar graphs, comparing active treatment to sham. Okay, we saw that. And then we also saw information showing that the effect was durable over a long period of time. I can't remember the specific time frame. But since that information was presented this morning, I'm just trying to get a feeling as to whether those studies were felt by you to not -- could not be included in your analysis because there is quite a discrepancy.

DR. EYDELMAN: Right.

DR. GOOD: That's my point.

DR. EYDELMAN: I believe my team has some backup slides that they would like to bring up.

DR. MIN: This is Lauren Min again.

This slide presents references that were presented this morning by the petitioners, and listed here are those that were not captured in our literature search. There are nine articles here, one that was not captured in our search because it was in a foreign language. There was one study that was unpublished data, two studies that were not indexed, two studies that

were in books, and three studies that we had no search terms in common with the studies.

Next slide.

And this is a list of papers that were -- that the petitioners referenced in their presentation, and these studies were also captured in our search, but they were excluded from our literature review for -- sorry, this is the one. So, it's not listed here by reason, but basically they were excluded in our search due to non-cleared use, non-journal articles, and three of the studies had no clinical application.

And this is a list of studies that were presented by the petitioners, and were also included in our literature review. And while the sponsor presented -- these studies presented positive findings regarding the effectiveness of CES, FDA would like to highlight some methodological concerns in these studies.

The study by Bystritsky in 2008. There are basic study design elements that are needed in effectiveness studies, as Dr. Park mentioned earlier. And while this study showed a significant decrease in anxiety, the study lacked a randomized trial design, there was no sham control group, and they only enrolled nine subjects. So, that's a very small sample size.

In the next study by Cartwright, as you can see from this list, it's missing most of -- all but one of these important design characteristics, and this was an insomnia study where participants reported very basically

that they slept better after receiving the CES treatment. And I would also like to note that in the Cartwright study there was no statistical testing performed whatsoever. They just reported how many patients felt -- how many patients reported better quality sleep.

The study by Gomez in 1979, they enrolled subjects who were undergoing methadone withdrawal, and the main finding of the study was that anxiety was considerably reduced in the CES group. But, again, many of these study design characteristics were absent, including eligibility criteria based on a DSM diagnosis, clinically relevant effective measures. It was not adequately powered, with a sample size of only 10 patients. No statistical testing was done, and there was no adjustment for confounders. It lacked predefined success criteria and durability of effect.

The next study by Hearst in 1996 reported improvements in depression. It was a mixed results study. It was a positive finding for depression, but there was no significant difference reported for the anxiety indication. And, again, regardless of the outcome of the study, you can see that there were serious methodological design issues in this study.

The study by Krupitsky in 1991 reported significantly improved measures of both depression and anxiety. However, it did not have an eligibility criteria based on DSM diagnosis, did not have clinically relevant effective measures, sample size was small with only 20 participants enrolled, there was no predefined success criteria, and they lacked any information on

durability of effect.

Next, a study by Overcash in 1999. They used electromyogram and finger temperature as measures of anxiety, and these are not validated measures for anxiety. However, they did report positive findings, a beneficial effect of CES on anxiety based on these measures. However, it was not a randomized controlled trial design. There was no sham control group. Eligibility criteria based on DSM diagnosis was not applied. There was no clinically relevant effective measure, and they did not have a pre-stated criteria for success.

Next, a study by Padjen in 1995. Their main finding was that CES is associated with reduced depression among substance abusers, and some of the study limitations in this study include clinically relevant -- the absence of clinically relevant effective measures and a predefined success criteria.

Next, the study by Philip in 1991. They reported significantly reduced anxiety. However, there was no clinically relevant effective measure used, and the sample size was quite small with only 21 participants enrolled. There was no predefined success criteria or any information on durability of effect.

Next is a Schmitt study published in 1986, and this study enrolled alcohol and poly-drug users and found that CES is associated with significantly reduced anxiety. However, they did not use a DSM diagnosis

criteria or a clinically relevant effective measure. Also there was no -- the statistical measures were not appropriate and there was no predefined success criteria or any evidence of durability of effect.

Next, a study by Smith in 1999. They reported a highly significant benefit of CES treatment in reducing symptoms of depression and anxiety. However, all but the last of these important study design characteristics were missing from this study.

And lastly the Weiss paper which was published in 1973. As the petitioner noted, this RCT reported considerable improvement in various measures of insomnia. They actually used a very good objective EEG measure for their outcome. However, it was a randomized trial and they did have a sham control group, but the masking was not carried out successfully. In addition, they did not have eligibility criteria based on a DSM diagnosis. They were not adequately powered, as only 10 subjects were included in this study. They did not have a predefined success criteria or any information or evidence for durability of effect.

DR. GOOD: Thank you for that very detailed presentation, Dr. Min.

DR. HURST: Dr. Yang, did you have a question?

DR. YANG: So, I'm trying to wrap my mind around the adverse events and how significant they actually are. So, in the more rare column you talk about the seizures, but what about the worsening of depression and the

situational anxiety? And please remind me what the rate of that was and the papers that you reviewed and how maybe it compares to the, you know, current antidepressant medications and their failure rate.

DR. MIN: As I mentioned in my presentation, it's difficult to speak -- discuss the adverse rates in terms of rates because, first of all, the sample size was very small in most of the studies and they had high attrition rates.

And so I have how many patients reported these severe adverse events, and there was one patient who reported increased situational anxiety, and that was from the Smith paper, and the worsening of depression symptoms in four patients, and two of these patients were -- they required hospitalization for suicidal ideation.

And in the Philip paper, as I mentioned before, there were two cases of new onset epileptic seizures, which previously I said that they occurred during a five-day washout period prior to CES treatment. And I think the important thing to note about that study is that it really speaks to the poor design of the study, I believe, that they would take very sick psychiatric inpatients with major depressive disorder, take them off of their medications and give them CES treatment at a time when CES has not been proven to be effective.

DR. YANG: Do you mind if I ask a clarification?

DR. HURST: No, go ahead.

DR. YANG: Okay. So, the two patients that were worse on the depression, what was the *n* on that paper, and were they also taken off their medications and that CES was used as a single treatment?

DR. MIN: I can get that information for you --

DR. YANG: Okay.

DR. MIN: -- and get back to you with that.

DR. ALEXANDROV: Just a clarifier. Were those patients in the control group or the active group?

DR. MIN: For which adverse event?

DR. ALEXANDROV: For the worsening of the symptoms.

DR. MIN: I'll have to get back to you on that answer.

DR. HURST: We have one last question from Dr. Fessler, and then we're going to move to the discussion phase, during which time we can address further questions to the FDA if issues come up.

DR. FESSLER: So, first let me apologize for the inflammatory nature of this question. And I'll address it to any of you.

Can you name me, honestly, any currently available device or product in the United States that would stand up to the rigors that you just listed for the device we're talking about today? I can't think of any.

DR. EYDELMAN: Yes.

DR. FESSLER: Name it.

DR. EYDELMAN: This is not the appropriate place or forum to

do so, as we can't compare.

DR. HURST: Okay, let's go ahead. At this point we'll begin the Panel deliberations structured around the FDA questions. This is a slight deviation from the agenda; however, I'd like to ensure that each question gets an adequate response and deliberation time.

Let me also mention that although this portion of the meeting is open to public observers, public attendees may not participate except at the specific request of the Panel Chair. Additionally, we request that all persons who are asked to speak identify themselves each time. This helps the transcriptionist identify the speakers.

What I'd like to do is just begin on my right and go around and just have people bring up issues that they'd like to discuss, and we can go back and forth with those issues and then just move right around the table that way.

Mr. Mueller.

MR. MUELLER: Thank you, Mr. Chairman. Yes. David Mueller here.

I guess the two issues I would like to bring up are that, first of all, the FDA presentation did not cover what they defined to be safety-related data. They purposely, I guess, did not review for us the 11 papers on animal studies, which is one of the main things for defining safety.

And the second topic is, on the FDA panel question, is the list of

potential adverse events. Is this a complete and accurate list? And I don't think it's accurate based on the only two seizures that were described, happened before the treatment actually was used.

So, those are my two discussion topics.

DR. HURST: Thank you, Mr. Mueller.

Does anyone on the Panel want to directly address those before we move on to another issue?

Okay, let's -- oh, I'm sorry. Go ahead.

DR. DORSEY: I concur with the comments about the safety risks.

DR. HURST: Anyone else?

Dr. Alexandrov.

DR. ALEXANDROV: Yeah, my comments would be fairly similar and in line with those that were just provided.

It's unclear to me, from the review, which group was involved in the worsening of the condition, and I'd like to know more about that.

And I also think that when you're looking at worsening of a condition, there's also some ownership on the part of the treating practitioner, in terms of following that patient, that sits outside the safety of a device. I think that needs to be acknowledged.

DR. HURST: Other comments regarding Dr. Alexandrov's point from the Panel?

Yes, Ms. Carras.

MS. CARRAS: It's Michelle Carras.

I'd just like to say that when I read this, my thought, as a patient, was adverse effects of some current treatments for psychiatric problems can cause worsening of the problems. So, if you consider that the treatments, as they exist, and as they're taken by people out in society, have an efficacy of 30 to 50% with a placebo rate of about the same, then it makes me wonder why the FDA is bringing this up as a concern.

DR. HURST: Other comments? Yes.

DR. ANDERSON: This is Karen Anderson.

And related to that, with Dr. Min's comment about doing research on various psychiatrically ill inpatients, I think that in many cases the first studies are done in treatment resistant depression, and those are often people who are hospitalized, so I don't know that it's irresponsible as long as the research is conducted in a proper manner to study psychiatrically ill inpatients.

DR. HURST: Thank you.

Dr. Fessler.

DR. FESSLER: Rick Fessler.

My comments -- obviously I've already made one of them. I think the rigor that we're asking of these studies and of this device is extreme, to say the least. I think we should be considering safety separately

from efficacy. I think they've demonstrated safety beyond any reasonable doubt. Efficacy, I'm not so sure of.

And, finally, to do a twofold thing of ignoring 30 years of history is just silly, and then to eliminate all of the available data because it is not typical in research papers to state your hypothesis -- and generally, that's implied by the research -- and it is not typical to state a predetermined endpoint; you're just looking for statistical significance, and you will state what that is. So, to eliminate papers based on that, I think, is just completely unfair.

DR. HURST: Other comments regarding that, some of these methodology issues? Yes.

DR. KOTAGAL: I just have a very simple comment, that the device is safe. There is really no convincing evidence of any potential adverse effects.

With regard to the stimulus parameter, we all know biologically there is variability, and we see that in some of the other devices, like the vagus stimulator, the amplitude, the frequency, the pulse. They all seem to vary in terms of what stimulus is going to produce the most optimum response.

So, that's all I had to say. Thank you.

DR. HURST: Other comments from the Panel regarding those issues?

Yes, Ms. Carras.

MS. CARRAS: Michelle Carras.

I was thinking that, as a new student of epidemiology and biostatistics, it's my impression that these types of study designs haven't been around that long, and this level of discrimination of study design is fairly new, so I think that should probably be taken into account, that maybe the FDA is expecting a higher standard; whether that's a valid way to assess things, I don't know.

DR. HURST: Thank you.

Yes, Dr. Alexandrov.

DR. ALEXANDROV: Not to mention, they didn't have to go through the PMA process, so there wasn't a lot of incentive to add rigor in terms of a design. But I don't think that I have really a lot of concerns in terms of safety. I'd go back to what Richard just said and say that my concerns are a little bit more along the lines of the effectiveness of the device.

DR. HURST: Dr. Anderson.

DR. ANDERSON: I concur. I would also say that the IRB ethical regulations at that time were different, so that maybe adverse events that were very low-grade were not reported. So, it may be that there were a lot of low-grade adverse events that were not required to be reported at that time.

I don't think that makes the device unsafe; I just think that's why we're not seeing the frequency of the usual headache, you know, fatigue-type of adverse events.

DR. HURST: Mr. Mueller.

MR. MUELLER: Yes, Dave Mueller.

Also, I'd like to point out, too, that even though, you know, the best case is this, a fantastic clinical study, the C.F.R. does allow us to look at reports of significant human experience. And in our documents we have pages of significant human experience, including generals, captains, corporals -- I don't remember all the ranks -- saying how the military is using this on the battlefield, in the hospitals there, as well when they get back. That, I also think, speaks reams of efficacy data showing a good effect, and I agree with everyone here saying there is no safety concern. Thank you.

DR. HURST: Thank you.

Yes, Dr. Stein.

DR. STEIN: Yeah, I think it sort of underlies the risks of relying too much on testimonials because, you know, during the break, I went and talked to several colonels in the active army and they told me -- and I told them what had been explained and that even the people that were said to have said those things, and I got back, you know, a colleague at Walter Reed who said, I checked with people in the outpatient psychiatric clinics, this is rarely being used.

I wasn't able to get a hold of Jim Kelly at NICoE; he hasn't responded yet. I asked about in-theater use, and he asked as many psychiatrists as he could get a hold of in the last couple of hours, and he said he's not aware of anybody who is using it. So, maybe there are other groups of people using it, but I don't think we can put too much stock in testimonials.

DR. HURST: Thank you, Dr. Stein.

Other comments?

DR. ARRIA: Just along those lines, I was struck by the lack of research being conducted by the DoD, given those graphs on that the use is skyrocketing, that it just seems that there would be some interest on the part of the DoD to conduct those studies. And it looks like all of the effectiveness studies were conducted so long ago, and there doesn't appear to be a match between the use of it and the number of studies being done to evaluate it. So, that sort of raised a red flag to me.

DR. HURST: Dr. Good.

DR. GOOD: I think that's an important point. We did hear that there are some ongoing studies, not a lot, but there are some DoD studies that are ongoing. Unfortunately, we don't have that information, and one of our charges is to make a decision based on the information we have available at the present time. That's unfortunate in some ways, but that's our charge.

Just to close off the safety issue, I personally am convinced that this is a safe device based on all the comments that colleagues have made

around the table. The only thing I'll point out is this issue about worsening of condition being treated because of ineffective treatment, because that is a potential concern, but you have to rely somewhat on the clinicians to make a decision, a reasonable decision, and one of the people in the audience made that comment.

Certainly, any clinician can make a wrong decision and use the wrong treatment for the wrong reason and you'd have a poor outcome, where the person gets worse. I wouldn't say this device is any different than a medication in that regard. So, I don't think that's a major concern, in my opinion.

DR. HURST: Dr. Stein.

DR. STEIN: The other thing about published literature that I think everybody knows, but I don't think anybody has actually said yet, is that, you know, things tend to be published if they're positive, so we can't really -- I mean, if there are 100 positive publications, it could be that there were 300 studies done where it didn't look good and nobody bothered to publish it. So, again, just looking at the literature, we all know there's a big bias towards publication of positive results.

DR. HURST: Ms. Carras.

MS. CARRAS: Michelle Carras.

I wonder if that holds for complementary and alternative medicine studies. I know that it's true for traditional medicine.

DR. STEIN: Well, I can tell you, as somebody who is an editor for a journal, it doesn't really much matter. It's still really tough to get anybody excited about negative studies. Maybe the first negative study, yes; after that, no.

DR. HURST: Thank you. Let's just go ahead and move around.

Dr. Evans, any comments or other issues that you would like to raise?

DR. EVANS: Yes. Scott Evans.

Let me first thank the petitioners and the FDA for all their hard work gathering and evaluating these data. I understand the complex nature of these proceedings, and I really appreciate all of the efforts.

Given the many years of use, I think that the data from personal experience of my clinical colleagues, as well as the testimonials here today, are of considerable importance. However, I would like to relay my concerns as I reviewed the data.

First of all, randomized clinical trials are the gold standard for evaluating the effects of any intervention, and so they are the studies in which I put the most weight. Now, the results of the trials were mixed, at least with respect -- or inconsistent, at least with respect to statistical significance. Some trials were positive, some were negative.

I would suggest that we might be able to elucidate this perceived inconsistency with further evaluation using Forest plots. It's

possible that the effect seen in non-significant trials and significant trials could actually be very similar, but the only way we're going to see that is by looking at effect estimates using confidence intervals.

The second piece about the randomized trials that were conducted, I think Dr. Min did a very nice job of displaying some of the concerns with the quality of the trials that were conducted. The reliability of randomized clinical trials are only as good as the quality under which they are conducted.

Many of the trials did not use reliable diagnostic criteria; many did not pre-specify hypotheses to be tested; many did not pre-specify outcome measures to be used; many did not utilize validated outcome measures; many were without masking or blinding, which is particularly important in disease areas like this, where the endpoints are patient reported outcomes and subject to patient manipulation.

These are fundamentals of clinical trials, and I actually disagree that they're not reported that way. If you check the CONSORT guidelines, which provides guidelines for how to report the results of randomized clinical trials, these are fundamental issues.

Secondly, we are, in large part -- written down the point that was just made -- we are, in large part, relying on publications in the medical literature for our scientific evaluation. Research is often selectively published, and we know there's an under-reporting of negative evidence;

that's known. Journals are not excited to report negative results. So, therefore, I think we just need to understand, or at least try to evaluate, whether what we're reading is representative of what's really happening or whether it's a selection of what's really happening.

And, in fact, we see some of that selection or optimistic reporting even within some of the trials that are reported. You see trials that are reported that report efficacy results without even a mention of safety outcomes. That's selective reporting. I mean, that's incomplete reporting. And so we have to be aware of that.

And I think this point about the reporting of safety data, you've got 30 -- or decades of use of these devices. And we get down to the question of is "absence of evidence" evidence of absence? Well, it is, if there is systematic follow-up -- and you could be assured that events would be reported if, indeed, they occur. Are we in that case? I don 't know. You can tell me. But right now, we cannot distinguish between no events happening versus they're not being reported. And having no data is not data of absence, and so I would be careful about that.

Thirdly, we're not talking about a specific device. I think it was Dr. Rosch, whose title to his talk was "Not All CES are Created Equal." If it is true that there is considerable heterogeneity across -- of effects of CES devices -- and there is some evidence of that, even in earlier discussions with dizziness and other side effects -- in addition to variable methods of

application, which we've seen about where they place electrodes and so on, then we have to be really careful about making blanket statements or umbrella statements about what's happening over a class of devices.

Lastly, it seems to me that patients that suffer from depression, anxiety, or insomnia may not have optimal use of their faculties. And this means that they are potentially a vulnerable population, which to me means that we need particular scrutiny in data evaluation. That's warranted to ensure protection of such patients.

So, those were my comments.

DR. HURST: Any comments from the Panel regarding Dr. Evans' points?

(No response.)

DR. HURST: Thank you. Let's move on.

Dr. Steier.

DR. STEIER: Yes, thank you very much. Ken Steier from New York.

I would, again, just mention that there have been cases where things have been thought to be safe and proved not to be, certain drugs: Thalidomide, Trovan, Phenformin, others, that were ultimately -- went through all kinds of clinical trials and fulfilled all the criteria we just talked about, but when actually released and used the way patients sometimes use things, in addition to a bunch of other variable factors that we can't control,

they subsequently caused fatalities and had to be pulled from the market. And everybody knew about that. So, that was well published.

So, in contrast, here we have a product that's been out for, again, 30 years, widely used, and we haven't really read about any significant safety issues or fatalities anywhere, which would make me think that probably it's a safe product.

In addition, many of the things we do in clinical practice in treating patients have not been substantiated anywhere through randomized clinical trials or anywhere else, but they're still done. They help patients; they save lives. We all do them, and we don't put them under this.

The problem here, I think, is really the timing. If this was a new product and it hadn't been out and people hadn't used it and we didn't have so many testimonials from people who seem to me to be very credible, you know, it would be one thing; but that's not what we have. And to try to work backwards, I think, and apply clinical trials to something that's already been out in practice, widely used, I'm not sure I understand how that really makes sense since the most important test is when it goes public and people actually use it.

DR. HURST: Thank, Dr. Steier.

Any Panel -- yes, Dr. Kotagal.

DR. KOTAGAL: Suresh Kotagal.

So, I appreciate Dr. Evans' point about vulnerable population

but, you know, there's also the issue of beneficence, and these are patients who are critically ill; very often, they're in a psychiatric hospital or locked area. And I think it's important for devices also to be available for vulnerable populations, so I guess that would be the flip side that I would submit.

DR. HURST: Thank you.

Dr. Anderson, any comments?

DR. ANDERSON: Yes. I continue to be concerned about the issue of concomitant psychiatric medication, so again, it would have been very helpful if the FDA could have specified whether the subjects in the different studies were on psychiatric medication at the time. To me, it's very different to specify something as a single agent treatment versus some kind adjunctive therapy. So, I think that remains a big concern in terms of efficacy.

I also share the concern of other Panel members about lumping depression, depressive symptoms, major depression into one category or doing the same with anxiety. I think that the population needs to be very well defined. I don't agree that depression or anxiety present the same way in all populations. I think they can be different in different patient groups.

DR. HURST: Thanks, Dr. Anderson and Dr. Kotagal.

We're going to move along here, so bring up points, but we want to leave plenty of time to directly address the FDA questions.

Any points?

(No response.)

DR. HURST: Does the FDA want to address those questions that were put at the beginning of our session?

DR. EYDELMAN: Thank you.

DR. MIN: This is Lauren Min.

I'll start by saying that the main purpose of our literature review was to evaluate the safety of CES, and so we did not pool all of the safety articles, but for the one article that I mentioned in which four patients reported worsening of depressive symptoms, this was a paper by Feighner and colleagues. And of the four patients, two were in the active CES treatment group and the other two were in the control group, and both got worse in their depressive symptoms after receiving their assigned treatment. And it's notable that they were still under psychiatric medications at that time.

DR. HURST: Thank you. Let's move along.

Dr. Dorsey.

DR. DORSEY: So, the main issue I have is that for the last 30 years, if not longer, the FDA -- its advisory committees repeatedly, in the literature, including that supplied by petitioners, has raised concerns about the efficacy of CES, and although there's a wide range of evidence that's been provided to it, in support of it, the greater the rigor of the study, the less likely that there are beneficial outcomes.

And there's a hierarchy of studies, and we shouldn't be, you

know, shy about stating that. And the greater the rigor of the study, the less likely there is to show benefit. And even the investigators, the petitioners, I think most petitioners, have cited, have repeatedly called for rigorous control studies to demonstrate its efficacy, and to my estimation, those have not been done. I think all that raises serious questions about reasonable assurance of efficacy of this device.

DR. HURST: Thank you.

Dr. Good.

DR. GOOD: I don't, at this point, have anything to add to what's already been said. Thank you.

DR. HURST: Thank you.

Dr. Yang.

DR. YANG: So, as far as safety goes, I think I agree with the majority, that I don't see anything that is reasonably unsafe here.

But as far as efficacy goes, of course, we're all aware of the methodological difficulties. My concern is more about the downgrading, though, because once this is downgraded, then my understanding is that any new substantially equivalent device would go through a 510(k), which means that you're comparing or "as good as." And if "as good as" is unclear what you're comparing to, then I don't know how you can downgrade.

DR. HURST: Thank you.

Dr. Arria.

DR. ARRIA: I don't really have too much to add from what's already been said. I definitely concur with almost all of the comments by Dr. Evans and Dr. Dorsey regarding their assessment of what has been discussed today.

I would just like to state my opinion is that I do not believe that the science is at a state of quality that we can make a determination of the effectiveness.

DR. HURST: Thank you.

Dr. Stein.

DR. STEIN: Yeah, Murray Stein.

Yeah, I agree with people about -- with most of the people about safety. I mean, if this device really has been used -- it has been used for as long and in as many individuals been described, I would think that if there were adverse effects that were new or highly prevalent, we'd hear about them and don't agree with a longer list of adverse events that the FDA has put forward.

In terms of efficacy, I guess, you know, I'm sympathetic to the fact that these devices have been on the market for a long time, and some people are clearly deriving benefit from it, but the studies that are 25 and 30 years old don't meet our 2012, sort of, standards for demonstrating efficacy, and that's no one's fault, but that's just the way it is. We've got to be working as a Panel, I think, in terms of, you know, in 2012 what would we

judge to be reasonable evidence of efficacy, and I don't think it's there.

DR. HURST: Thank you.

At this time, let's focus our discussion on the FDA questions. Copies of the questions are in your folders. And I'd like to remind the Panel that this is a deliberation period among Panel members only. Our task at hand is to answer the FDA questions based on the data in the panel packs and presentations we heard this morning and the expertise around the table.

With that said, we'll show the questions, and I'll ask each member, Panel member, to identify him or herself each time she speaks again. And we can then just go around the table again.

Please show the first question.

MR. MARJENIN: Question Number 1: For the indications of "insomnia, depression, and anxiety," FDA has identified the following key risks of CES from the review of the public docket, Manufacturer and User facility Device Experience (MAUDE) database, and FDA's literature review, shown here on the next slide.

a. Worsening of the condition being treated as a result of ineffective treatment
b. Potential adverse effects from electrical stimulation of the brain
c. Potential risk of seizure
d. Skin irritation

e. Headaches

f. Blurred vision

Is this a complete and accurate list of the most significant risks presented by CES? Please comment on whether you disagree with the inclusion of any of these risks, or whether you believe any other risks should be included in the overall risk assessment of CES.

DR. HURST: Let's begin again with Mr. Mueller and work our way around.

MR. MUELLER: Okay, David Mueller.

I disagree that it is an accurate list. If these are the major -- (a) was, we said, the worsening of conditions? No.

Electrical stimulation, potential adverse events from electrical stimulation of the brain. There's nothing really known right now.

Seizures, the only seizures known were in the article where it happened to patients who have not been exposed to the treatment.

Skin irritation, maybe.

Headaches, there are no reports.

And blurred vision, no, because that was when they were, a long time ago, stimulating on the eye. Now, theoretically, yes, you could put that on, but I think with the labeling we have today, it could be said don't put it on the eyes.

DR. HURST: Thank you.

Dr. Alexandrov.

DR. ALEXANDROV: I would concur, except that I would say that, in terms of potential adverse effects from electrical stimulation of the brain, I'd say we just don't know the answer to that because I don't know that we have a lot of data to support any type of longitudinal study of what happens to people that use this continuously over a long period of time.

DR. HURST: Thank you.

Ms. Carras.

MS. CARRAS: It's Michelle Carras.

I would have to say I agree only with skin irritation, but I would possibly add transient dizziness.

DR. FESSLER: I'm pretty much in line with everyone else. I think I agree with skin irritation and headaches, and the rest I do not believe we have demonstrated significantly that they are risks.

DR. HURST: Dr. Evans.

DR. EVANS: Yeah, I don't have any comments to add.

DR. HURST: Dr. Steier.

DR. STEIER: I'd go with skin irritation.

DR. ANDERSON: I'd go with skin irritation, headaches, and the potential adverse effects from electrical stimulation of the brain.

DR. HURST: Dr. Kotagal.

DR. KOTAGAL: I would suggest omitting the potential risk of

seizures and blurred vision.

DR. DORSEY: Skin irritation, headaches, vertigo, depending on placement of electrodes. I think that's it.

DR. HURST: Dr. Good.

DR. GOOD: Yeah, I agree with skin irritation. I don't think the risk of seizures is real. And I'm not sure about the potential adverse effects. I guess the animal data would be helpful in that regard, which you really haven't reviewed in detail. But perhaps potential risk of seizures, dizziness, maybe -- I'm sorry. Sorry, take it back. Skin irritations, headaches, and possibly dizziness.

DR. HURST: Dr. Yang.

DR. YANG: I agree completely with Dr. Good. Skin irritation, headaches, and dizziness.

DR. HURST: Dr. Arria.

DR. ARRIA: I'd like to concur with the rest of the Panel. I'd sort of like to emphasize that I think that for the first -- for worsening of the condition criteria, I think that more longitudinal studies need to be done to look at patient populations who are or are not using other adjunctive treatments or more traditional pharmacotherapies for the condition in order to determine whether or not that's true.

DR. HURST: Dr. Stein.

DR. STEIN: Skin irritation, headaches, and dizziness.

DR. HURST: So, I get the sense that the Panel is in pretty good consensus here that skin irritation, headaches, maybe dizziness. Worsening of the condition certainly is a very concerning thing, but probably will require longitudinal studies if we really want to look at that. And very importantly, probably is addressed by having the device used under the supervision of a physician or someone following the case.

So, my sense is that this does not seem to be a complete and accurate list of the most significant risks.

MR. MARJENIN: Thank you.

Question 2: As defined in 21 C.F.R. 860.7(e)(1), there is a reasonable assurance of effectiveness if there are clinically significant results in a significant portion of the target population when the device is used for its indications for use and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use. FDA believes the available scientific evidence does not demonstrate that CES will provide a reasonable assurance of effectiveness for the indication of insomnia, depression, or anxiety; and so

a. Please comment on the adequacy of the available scientific evidence in defining a clinically accepted target population for CES and the relationship between this population and the indications for use, "insomnia, depression, or anxiety."

b. Does the scientific evidence support a reasonable assurance of effectiveness for the indications for use of "insomnia, depression, or anxiety"?

DR. HURST: Okay, those questions are slightly different than the ones that I have written down here and I think are slightly different than what the Panel has. The sense of the questions seem to be identical; it's just the wording is a little bit different.

So, we can go ahead, I think, and begin with Mr. Mueller and move around the table.

MR. MUELLER: Yes, David Mueller.

I believe that using the full definition of valid scientific evidence from the C.F.R., it definitely provides valid scientific evidence that it is efficacious for insomnia, depression, and anxiety, Part a.

And Part b, reasonable assurance based on the presentation that the reasonable assurance -- I'm sorry. Efficacy and the significant portion of a target population that will provide clinically significant results; yes, I say it does.

DR. HURST: Thank you.

Dr. Alexandrov.

DR. ALEXANDROV: I would disagree. I don't think that there are data that suggests that the device is effective. I don't think the quality of the data available are as good as they should be for us to be able to make

that determination and, therefore, I find it difficult to support that there is reasonable assurance of effectiveness.

DR. HURST: Thank you.

Ms. Carras.

MS. CARRAS: This is one that I have a really hard time with. First, our questions say for the indication of "symptoms of insomnia, depression, or anxiety," and I understand, from -- I think it was Paragraph (f) that you referred to, that there is more clear guidance about whether there's a clinical diagnosis necessary to indicate a valid target population, but that part is confusing to me.

And as a person with a mood disorder, I would have to say that I'm very aware that the same symptoms that I have are shared by many people in the population at various times, and as a Patient Representative, I have to question whether the target population needs to be defined by a clinical diagnosis or if it's acceptable to say "symptoms of depression, insomnia, and anxiety" without specifying a clinical population.

MR. MARJENIN: This is Tim Marjenin.

The version of the question as it appears on the slide is correct. So, the indications for use, insomnia, depressions, or anxiety without the phraseology "symptoms of" and yes, you are correct that Paragraph (f) of the section regarding well-controlled investigations does discuss having a well-defined patient population.

DR. EYDELMAN: I would like to draw your attention to Slide Number 10, which Dr. Park presented. I think that is what you are referring to, and that clarifies the issue that you're addressing.

MS. CARRAS: So, I'm sorry. I guess I'm confused about whether the evidence describing the target population necessary has to do with the clinical studies that are presented or the indication that we would be classifying, recommending classification for.

DR. EYDELMAN: So, if I can jump in here. I think the confusion is we're trying to say that the intended -- the indications for use needs to identify population with these disorders.

DR. HURST: Yes.

MS. CARRAS: I'm sorry, one final point.

I just wanted to say that in the classification of electroconvulsive therapy, there is no clinical diagnosis associated with that, it says, for depression.

DR. HURST: And would you say that you -- what are your answers to those two questions?

MS. CARRAS: I'm sorry.

Well, I guess we're given two different wordings, so if the slide is the correct wording -- sorry, I have to -- can you put the slide up? Third, I don't see a clinical diagnosis on there, so I would have to say yes, it does provide evidence of effectiveness.

DR. HURST: Dr. Fessler.

DR. FESSLER: My answer to (a) would be yes. My answer to (b) would be no. I think our evidence is still a little bit weak.

DR. HURST: Dr. Evans.

DR. EVANS: I haven't been convinced of the effectiveness. Although I was impressed by many of the testimonials that were shared today, I guess when I'm pressed with sort of conflicting results, I'm going to go to randomized trials to -- that's, you know, the gold standard study that's going to have the most weight for me. So, I would say no.

DR. HURST: So, you agree with their conclusion? You say that it does not support? Very good.

Dr. Steier.

DR. STEIER: I would say, from what's on the screen, I'm a little confused, I admit. But from what's on the screen, I would say yes and yes.

DR. HURST: Thank you.

Dr. Kotagal.

DR. KOTAGAL: For (a), I would say yes.

For (b), I would have to break this down into, first, the depression. A clinically accepted target population that might -- the efficacy, yes, has not been -- I mean in terms of -- sorry. I'll take this back.

Does the scientific evidence support a reasonable assurance of efficacy in depression? I would say no.

For anxiety, I would say yes. Subjects with anxiety of different categories seem to benefit from the device.

With regard to insomnia, I would state that if sleep is disrupted from anxiety -- in other words, this is a comorbid insomnia from anxiety, it might show benefit. With regard to primary insomnia, there is no evidence.

DR. HURST: So, you feel that the evidence is mixed with respect to the different indications?

DR. KOTAGAL: Correct.

DR. HURST: Okay.

DR. KOTAGAL: Yes.

DR. HURST: Okay.

DR. KOTAGAL: I feel it does work for anxiety.

DR. HURST: Okay.

DR. KOTAGAL: It does not work for depression.

DR. HURST: Dr. Anderson.

DR. ANDERSON: With regard to (a), I feel that we have not defined the target population adequately, again, due to the lack of gold standard diagnosis and the mixing of definitions of these symptoms in the studies.

With regard to (b), no, I don't think the scientific evidence supports this.

DR. DORSEY: I agree with Dr. Anderson.

DR. HURST: Dr. Good.

DR. GOOD: So, for (a), I do not think that there is a clinically accepted defined population. We have primarily symptoms of depression, anxiety, and insomnia, and there they can be reflective of many different disease entities, so I don't think that there is a specific target population.

We heard all sorts of specific diagnoses from PTSD to fibromyalgia to a variety of other conditions, all of which may help. They have the symptoms of depression, anxiety, and insomnia as part of their components. So, I would say the answer to (a) is no.

For (b), I don't think there's any scientific evidence to support reasonable assurance of effectiveness. Again, we talked about the design problems of the studies. It is unfortunate that we're in a different era now than the '70s. I agree with that. It's unfortunate for the petitioners in some ways, but that's where we are today. And so I think we have to go with, as was stated earlier, with what -- with 2012. You know, I'm impressed, also, by the testimonies and anecdotes. I think they're strong. But we can't make decisions on that basis.

The other thing I'm concerned about is that there's really no clear mechanism of action here. And as a clinician, I would like to know exactly how CES really works, what's the effectiveness. You like to have a specific type of mechanism, and it's not here.

DR. HURST: Dr. Yang.

DR. YANG: I don't have any additional comments to add. No for (a) and yes for (b).

DR. ARRIA: I don't have any additional comments. I would say no for both questions.

DR. HURST: Dr. Stein.

DR. STEIN: I'm just going to take the Fifth on (a) because I'm really not sure what it means.

But on (b), I'd say no, I don't think that there's sufficient evidence to really know if it works or not. I mean, given what I've been hearing today through the testimonials and, you know, by virtue of the fact that these treatments have been used for 30 years, I really would love to see well-conducted trials done to see if these treatments really can be effective for these conditions.

DR. HURST: Dr. Yang, you had another comment?

DR. YANG: Yes, I did. I apologize. I was reading the paper, not the slide. So, I think what I really meant to say was I do not think that the scientific evidence supports reasonable assurance.

DR. HURST: Thank you.

So, my sense is that -- yes, Dr. Alexandrov.

DR. ALEXANDROV: I just wanted to comment that it would seem that, based on the evidence that exists, that the definition in the community of users is different than the FDA's definition that sits here for

primary diagnosis. And I just think that that's important to point out.

DR. HURST: Yes, Mr. Mueller.

MR. MUELLER: Dave Mueller.

Just one quick point regarding mechanism of action. There are many neurological devices that we do not know the mechanism of action. Deep brain stimulation for Parkinson's for tremor; spinal cord stimulation for chronic pain; peripheral nerve stimulation for chronic pain. We know the theory, but we don't know mechanism.

DR. HURST: Yes, Dr. Stein.

DR. STEIN: I'll just echo that. I actually wanted to add that I'm a psychiatrist. If we waited to accept treatments only when we knew how they worked, we really wouldn't have anything. So, it would be nice to have, but I'm not bothered by the absence of mechanism here. I just want to see data on efficacy.

DR. HURST: Thank you.

My sense is that the Panel has a pretty good consensus that the adequacy of the evidence for defining a clinically accepted target population is perhaps mixed, but probably not adequate.

And similarly for (b), the scientific evidence to support a reasonable assurance of effectiveness for the indications or use for insomnia, depression or anxiety are, again, not adequate in the minds of the majority of the Panel.

And that also, I probably should put in there, because it has been mentioned and I think it is important, that there are a number of devices, particularly with respect to the nervous system, that we don't know the mechanism of. So, that while we would like to know the mechanism of them, that's not a fatal flaw simply that we don't.

Thank you.

DR. EYDELMAN: Thank you very much.

Question 3.

MR. MARJENIN: Question 3: Based on the available scientific evidence, do the probable benefits to health from the use of CES for these indications (meaning treatment of insomnia, depression, and anxiety) and conditions of use outweigh the probable risks?

DR. HURST: In this case, I'm going to begin with Dr. Stein, and we're going to work our way back around, just to mix things up and keep everyone on their toes here.

DR. STEIN: No.

DR. HURST: Thank you.

DR. ARRIA: No.

DR. YANG: No.

DR. GOOD: No.

DR. DORSEY: No.

DR. KOTAGAL: Once again, I will break my responses up. For

depression, no; for insomnia, no; for anxiety, yes.

DR. ANDERSON: No for all.

DR. STEIER: Yes for all.

DR. EVANS: No.

DR. FESSLER: You know, this is a tough one. There are no significant complications, so it's hard to not outweigh it even if there's no proven benefit. So, I kind of have got to go yes on this one.

DR. HURST: Ms. Carras.

MS. CARRAS: Patients are looking for treatments. Many of us are resistant to many different treatments. There seem to be little to no risks for this one. So, I would say absolutely.

DR. ALEXANDROV: No.

DR. HURST: Mr. Mueller.

MR. MUELLER: I would say definitely yes, given the low risk and probable benefit.

DR. HURST: And my sense is there is a preponderance of noes with respect to this question. There certainly are a number of Panel members with some reservations, primarily based on what appears to be -- and correct me, I don't want to put words in anyone's mouth, but almost a complete lack of safety concerns with this device. We don't see any safety problems whatsoever. Based on that, at least, that was what was articulated, a number of the members would answer yes to this question, but the

majority favor no.

DR. EYDELMAN: Thank you.

Question 4.

MR. MARJENIN: Question 4: The petitioner believes that a reasonable assurance of safety and effectiveness can be provided for the indications of "insomnia, depression, or anxiety" through the general controls that are required for all medical devices, and through the use of the following special controls. These proposed controls would not address the variability in the stimulation characteristics or electrode placement.

- Limited postmarket surveillance (e.g., physician and patient surveys)
- Adequate instructions for use, including warnings about the possibility of unsafe use
- Available only upon the order of a health care professional licensed to diagnose and differentiate the primary indications of CES for anxiety, insomnia, and depression from other disorders
- Compliance with voluntary consensus standards, including those for electrical safety, electromagnetic compatibility and interference, and quality systems

Please discuss the following three items:

a. The adequacy of these proposed controls in providing a

reasonable assurance of safety and effectiveness in light of the available scientific evidence.

b. In light of the scientific evidence, which stimulation characteristics (including electrode placement) and parameter ranges of CES treatment you believe to be the most important factors contributing to effective treatment.

c. Any additional controls you believe could be included.

DR. HURST: I'm going to ask that we begin with Dr. Stein again and work our way around the table.

DR. STEIN: Yes. I mean, some of these questions aren't so relevant, if I don't believe that there's evidence of efficacy. So, I don't have safety concerns, so, you know, what's proposed in terms of limited postmarketing surveillance, instructions for use, prescribing by professional, compliance with the standards are all fine in terms of safety. Those make sense to me. And they're adequate. But I couldn't say anything based on the scientific evidence I saw about what stimulation characteristics would make most sense. And I wouldn't have anything else to say about additional controls.

DR. HURST: Thank you.

Dr. Arria.

DR. ARRIA: I agree with Dr. Stein. I just have a sense of

confusion around the parameter ranges of CES treatment that are not adequately specified. I'm still not clear on how it is to be used in a clinical setting; maybe it's because I'm not a clinician. But as a layperson, I really don't understand that from the discussions today. So, I don't see that there's been adequate description of those parameters.

DR. HURST: Dr. Yang.

DR. YANG: So, for (a), similar to Dr. Stein. I don't have issues about safety, so those labels are fine. Effectiveness, we just spoke about.

(b), I have no idea. Based on the evidence that we have right now, I have absolutely no idea.

And (c), I don't have anything significant to say.

DR. HURST: Thank you.

Dr. Good.

DR. GOOD: Well, again, I agree with Dr. Stein. And since the answer to 3 is no, this is kind of -- these are all kind of moot questions. If the answer to 3 was yes, then these questions make sense. And, again, I really don't know anything about the parameters; we didn't really get enough information to draw any conclusions or make any recommendations about that.

If this were reclassified to a Level II device, then I would suggest that the instruction information for the patients to be revised because I think they're somewhat misleading.

DR. HURST: Thank you.

Dr. Dorsey.

DR. DORSEY: Similar comments that have been raised earlier. The controls don't give me reasonable assurance of effectiveness. They're just lacking evidence.

DR. HURST: Thank you.

Dr. Kotagal.

DR. KOTAGAL: The device should receive Class II approval for the treatment of anxiety disorders. For this indication, the general precautions stated should be sufficient.

Additionally, however, I would like to add that the device should not be used in subjects below the age of 18 or those with a known history of seizures and that they be followed up 60 to 90 days later.

For depression and primary insomnia, I feel it should still stay as Class III.

DR. HURST: Thank you.

Dr. Anderson.

DR. ANDERSON: I agree that the device is very safe. I wouldn't propose any more controls. I think we can't comment on the stimulation parameters because we really weren't given enough information on that due to the nature of the trials that were done. And no additional controls.

DR. HURST: Thank you.

Dr. Steier.

DR. STEIER: Dr. Steier.

Since we all agree that there's essentially no risk, if there was even one patient benefitted, it would seem like there would be more efficacy than risk.

I also know the device, itself, runs on two triple A batteries, which is the same as my TV remote control at home, and that's usually pretty safe except when my kids keep changing channels on it. So, I think it's fine, and I don't see any problem with these limitations.

DR. HURST: Thank you.

Dr. Evans.

DR. EVANS: I agree with Dr. Steier. I don't have anything further to add.

DR. HURST: Dr. Fessler.

DR. FESSLER: I completely agree. I think the proposed controls are fine. Sub-clinical electrical stimulation, whether it's magnetic or electrical, is something we just don't know anything about, so there's really nothing we can say about (b).

DR. HURST: Ms. Carras.

MS. CARRAS: I have a question for Dr. Eydelman about postmarket surveillance. I wonder if there are any other forms other than physician and patient surveys.

DR. EYDELMAN: I'm going to ask Dr. Krulewitch to comment.

DR. KRULEWITCH: I'm Cara Krulewitch. I'm the Branch Chief in the Division of Epidemiology.

Can you give me a little more with your question as to what you want to know?

MS. CARRAS: I understand that it's not commonly done in psychiatric conditions, but I know that for some conditions there are things like registries, and I was wondering if there were any other forms that postmarketing surveillance might take.

DR. KRULEWITCH: If the device is a Class III device, FDA can mandate a postmarket study, and it can be either in the form of registry or any other type of clinical study.

If the device is a Class II device, the mechanisms for postmarket surveillance of the device would be passive reporting through our MDR reporting system and surveillance of the literature. We don't normally -- we cannot mandate them if it's Class II unless, through our other surveillance methods, we identify a serious public health concern.

DR. HURST: I'm sorry, go ahead.

MS. CARRAS: In that case -- let's see. I would have to say for (a), there is -- the proposed controls are adequate.

I would have to say that for (b), the clinician should be able to decide the parameters as they do with electroconvulsive therapy.

And I don't think there are any more specific controls needed.

DR. HURST: Dr. Alexandrov.

DR. ALEXANDROV: I agree with the comments made on the opposite side of the table, that because of the problems with the effectiveness data, that I cannot really comment on these.

DR. HURST: Mr. Mueller.

MR. MUELLER: Yes, Dave Mueller here.

I agree with our Patient Representative, and I would also like to point out that there is another option that has not been brought up by FDA, which is that for a 510(k), FDA can require clinical data in the 510(k). So, we could classify it Class II. And then for new devices that come up, they could be -- have clinical data that would demonstrate they are as safe and effective as the existing devices.

Dr. Eydelman.

DR. EYDELMAN: You are correct in that many 510(k)s have clinical data. However, for the purposes of finding substantial equivalence for these devices, if it would be within the same range of parameters as is currently -- is currently one of the marketed devices, most likely clinical data would not be requested should it go to the 510(k) route.

DR. HURST: So, my sense, from the Panel, is that while the adequacy of the proposed controls for providing reasonable assurance of safety are fine, there are some significant questions regarding effectiveness,

which kind of makes it a moot question.

Dr. Kotagal did mention that for anxiety, he did feel that these proposed controls provide a reasonable assurance of both safety and effectiveness; however, not for the other two indications.

And, again, I think that there are a lot of questions in everyone's mind as to which stimulation characteristics we would believe to be the most important factors. I just don't think that anyone knows enough to make those statements with a great deal of certainty.

And no one suggested any additional controls except for the possibility of requiring clinical data on follow-up of 510(k)s should this become Class II.

DR. EYDELMAN: Thank you for that summary.

Question 5.

DR. HURST: Before we go on to Question 5, why don't we go ahead and take our break? And I believe that it's going to be a 20-minute break, and again, we'll just caution everyone not to discuss the subject to anyone during the break.

Thank you very much.

(Off the record.)

(On the record.)

DR. HURST: Yes.

MR. MUELLER: Just a follow-up to Dr. Stein's earlier comments

where he had e-mailed or talked to colleagues in the armed forces and he got some information back, but couldn't get it quickly enough.

There is a Colonel Pastal (ph.) here from the armed forces who is willing to discuss what the experience of the military is as a follow-up to Dr. Stein's earlier comment. So, I'm just wondering if Colonel Pastal could make a comment regarding the military's experience for what Dr. Stein had talked about earlier.

DR. HURST: I think at this point, we're not any longer open to public comment. So, let's hold off on that.

MR. MARJENIN: Question 5: Based on the available scientific evidence and the proposed special controls, what classification do you recommend for insomnia, depression, and anxiety?

DR. HURST: Let's again begin with Dr. Stein, please.

DR. STEIN: So, I'd recommend Class III for all three of those.

DR. HURST: Thank you, Dr. Stein.

Dr. Arria.

DR. ARRIA: Class III for all three.

DR. HURST: Dr. Yang.

DR. YANG: Class III for all three.

DR. HURST: Dr. Good.

DR. GOOD: Same. Class III for all three.

DR. HURST: Dr. Dorsey.

DR. DORSEY: Likewise, III.

DR. HURST: Dr. Kotagal.

DR. KOTAGAL: For insomnia and depression, Class III. For anxiety, Class II.

DR. HURST: Dr. Anderson.

DR. ANDERSON: Class III for all three.

DR. HURST: Dr. Steier.

DR. STEIER: Class II for all three.

DR. HURST: Dr. Evans.

DR. EVANS: Class III for each.

DR. HURST: Dr. Fessler.

DR. FESSLER: Class II for all.

DR. HURST: Ms. Carras.

MS. CARRAS: If we recommend Class III, we're going to be putting this in the same class as pulse generators, implantable pacemakers, breast implants, AEDs, and we seem to concur on the fact that there is no safety problem with it, so I don't understand how it could even go in Class III. It's not life threatening or life sustaining. So, I recommend Class II.

DR. HURST: Dr. Alexandrov.

DR. ALEXANDROV: Class III for all three, but I would also add that I think we need to come to some clarity about whether we're going to use this for symptoms or the primary diagnosis. I think that's still very, very

unclear.

DR. HURST: Mr. Mueller.

MR. MUELLER: Dave Mueller.

Class II for all three. And I would like to add that the -- I agree with our Patient Rep, that this -- I just can't see it being a Class III device.

DR. HURST: Thank you.

My sense is that the Patient Representative, the Industry Representative, and two of the voting members of the Panel believe that all of the indications should be Class II.

The remainder of the Panel believes that all of the indications should be Class III with one exception, who believes that anxiety should be Class II and depression and insomnia Class III.

DR. EYDELMAN: Thank you very much.

And now the last, final question, Number 6.

MR. MARJENIN: Question Number 6: Two of the three petitions FDA has received discuss the following indications for use: "the treatment of depression, anxiety and insomnia in adult substance abuse patients who have failed to achieve satisfactory improvement from one prior antidepressant or sleep medication at or above the minimal effective dose and duration in the current episode, or are unable to tolerate such medication."

And after the discussion, we would like to include in that the

indications that I mentioned earlier from Dr. Paros of Neuro-Fitness, the additional indications that he had stated in his petition further on, aside from the official pages. So, "CES is indicated for the treatment of primary symptoms of substance abuse, anxiety, depression, and insomnia when conventional approaches have failed or are deemed inappropriate."

And also, "CES is indicated for the general treatment of anxiety, depression, and insomnia as part of an approved program of medical care when conventional approaches have failed or are deemed inappropriate."

So, I realize that your slides do not reflect this, but I would like you to include this in your discussion. And so I can leave this up on the slide after I finish up with the additional points for this question.

So, while these statements include the indications provided by the regulation (depression, anxiety, and insomnia), FDA does not believe that these are the same indications that are identified in the regulation, nor have we evaluated these indications in marketing applications. Do you agree that these indications represent patient populations that are different from those that are described in the regulation: "insomnia, depression, or anxiety"? Please consider the following in your response:

a. Do these indications adequately define a target population?

b. What are the similarities and differences in the diagnosis, treatment, and ongoing management of

insomnia, depression, and anxiety in substance abuse patients versus insomnia, depression, and anxiety in those who are not substance abusers?

c. Do the characteristics of this population alter the risks of worsening of the condition being treated, adverse effects from electrical stimulation of the brain, seizure, skin irritation, headaches, and blurred vision? Are there additional risks that should be considered for these indications?

d. Does the available scientific evidence adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses -- anxiety, depression, and insomnia in adult substance abuse patients including also the indications that I just posted -- and conditions of use?

e. Does the available valid scientific evidence demonstrate reasonable assurance of effectiveness for these indications, inclusive of these additional indications?

So, if you would like me to leave this up here on the slide, I will do so.

DR. HURST: Oh, yes. If you would, please, leave them up. I'm going to start with Dr. Anderson and we'll just move right

around the table this way. This is a little bit of a complicated set of questions, so I'll give you a minute or two if you want to address all of them.

My understanding is that this primarily differentiates the substance abuse population from the non-substance abuse population.

MR. MARJENIN: That is correct.

DR. HURST: Okay, very good.

DR. ANDERSON: Karen Anderson.

No, I don 't think this adequately defines a target population. I think that substance abuse encompasses a very wide range of individuals, and certainly the duration, type of substance abuse, and severity can all be quite variable. And also whether they've had prior treatment or not for psychiatric symptoms. So, I'd say no to (a).

As far as (b), I think there are differences in the diagnosis and treatment of insomnia, depression, and anxiety in patients. Substance abuse, certainly, the effects of the drug and the substance are the obvious differences, but I think, you know, there are many social and other issues that can come into play with patients who are substance abusers. I can go into more detail if you want.

I don't think that there are worse -- that there are risks of worsening the condition with CES, but I don't see any additional risks that would be considered since we've established that it's a very safe treatment. And I don't see evidence that this is going to be effective, though.

DR. HURST: Thank you.

Dr. Steier.

DR. STEIER: I have a slightly different take.

Substance abuse, of course, is a very severe problem, very sad problem, and really there's very few therapies that provide any real long-term success, especially past the teenage years in terms of substance abuse. And we did hear a very, I thought, compelling discussion from the founder and CEO of Phoenix House, which is a very widely known substance abuse program, which has very good results.

So, under (a), I would say yes, it does define a target population of substance abusers. For instance, the people who go to Phoenix House. They may use different things, but there's a lot of similarities, as well.

(b), I think it's similar. Many have comorbid conditions, insomnia, depression, anxiety, in relation to their substance abuse.

(c), I say no. I don't think that there's any risk than anybody else.

Under (d), I would accept the scientific evidence that was presented by the Phoenix House and others.

And under (e), I would say yes, as well.

DR. HURST: Thank you.

Dr. Evans.

DR. EVANS: I do agree that this indication is a different patient

population than that described in the regulation. I don't think, at least in my eyes, I haven't seen enough focused analysis to know whether the benefits and harms might vary over -- depending on whether there's substance abuse users across that population of patients. I think we're in the same situation that's -- you know, we agreed that the risks are relatively minimal, but that there isn't proven efficacy.

DR. HURST: Thank you.

Dr. Fessler.

DR. FESSLER: In response to (a), I would say it probably does adequately define the population. And my reason for saying that is that, as a physician who uses many devices in my surgery, it has come to the point where what many devices are approved for is so narrow and so antiquated that they're no longer used for that and what has become standard of care is off-label uses. So, I think being extremely rigid in defining populations and uses is a double-edged sword. And I think in this case, I think it does adequately define a reasonable population.

I do not treat these patients, myself, so I do not have an answer to (b).

In terms of the characteristics of the population for risks, no, I don't think this increases risk to them.

Does the available evidence demonstrate the absence of unreasonable risk? Yes.

Does the available evidence demonstrate reasonable evidence of effectiveness? No.

DR. HURST: Thank you.

Ms. Carras.

MS. CARRAS: I would have to say yes to (a). This does seem to be comparable to how other indications are worded.

Similarities and differences: people with substance abuse disorders, I believe, have a little more stigma about the possibility of having a comorbid psychiatric illness or symptoms. They may prefer non-drug treatments, and because of their substance abuse, they may benefit from non-drug treatments.

I don't think they have greater risks, so no to (c).

Yes to absence of unreasonable risk of illness or injury.

And yes to effectiveness.

DR. HURST: Thank you.

Dr. Alexandrov.

DR. ALEXANDROV: I would say this is an adequate definition of a target population, but I agree with everything that Richard Fessler just said. In fact, I keep thinking it's kind of like if you're approving a hypertensive agent. You don't approve the hypertensive agent just for use in stroke, you don't approve it just for use in heart disease; you just approve the hypertensive agent. And I think that there should be some consideration in

the future, as these companies go forward, to think about using a definition that's more symptom based.

And with that in mind, I will also add that I am no one with expertise in this practice, and so I really can't respond to (b), but I do respect what Michelle just said because I think that's true, that substance abusers may be more successfully treated with something that is not drug based, although we have no data right now to suggest that.

I don't know that there would be any additional risk. I don't think that there are any data that would really help me to answer that question, though.

I don't think that there is, in terms of (d), any data currently available that tell me that it would be unreasonable risk, though.

And in terms of (e), I do not believe that there is valid scientific evidence right now for effectiveness.

DR. HURST: Thank you.

Mr. Mueller.

MR. MUELLER: Yes, David Mueller.

Regarding (a), does this indication adequately define a target population? I would say yes, it definitely does. While I personally think the current C.F.R. requirement, the broad statement, is definitely adequate, the way this is stated for the abuse patients would definitely work.

(b), what are the similarities and differences? I agree, again,

with Ms. Carras, the patient rep.

As far as (c), do these characteristics of this population alter the risks of worsening the conditions of treated adverse events from electrical stimulation on the brain, such as seizures? We've already said that, again, there is really no risk to this population, and I still can't, for the life of me, understand how "seizures" was originally put in here when the only reference came from patients who weren't treated with the device. I just can't understand that.

So, (d), does available scientific evidence adequately demonstrate? Yes.

And (e), valid scientific evidence, definitely, yes.

DR. HURST: Dr. Stein.

DR. STEIN: So, I think it defines a target population better than the more open-ended one before only because it narrows it down to a group of patients with substance abuse, but I still don't think it's adequate in terms of talking about the kinds of depression or anxiety or insomnia, the diagnoses associated with that.

Agree with what many others have said about there being some differences in treatment of these conditions in patients with substance abuse disorders. And in my experience, they can be more difficult to treat for their anxiety and depression and insomnia, and having some non-drug treatments that work would be extremely valuable, so I hope those studies

take place.

Do the characteristics of this population alter the risks? I don't think so.

Does the available scientific evidence demonstrate the absence of unreasonable risk? I believe the answer is yes.

And in terms of the scientific evidence demonstrating reasonable assurance of effectiveness for this indication, I want to point out that this indication is an even higher hurdle than what we've heard about before because this suggests that the treatment would work in people where other treatments have failed. So, we have, as far as I can tell, absolutely no evidence of that.

DR. HURST: Thank you.

Dr. Arria.

DR. ARRIA: I agree with Dr. Stein and Dr. Anderson. I think their answers were pretty consistent.

I'd just like to emphasize their point about the clinical presentation of anxiety, depression, and insomnia being more complicated because the research shows that substance use disorder patients are highly heterogeneous, and there's a high possibility that in a majority of patients there could be preexisting conditions, and for another set of patients it could be a result of the substance use disorder, and whether or not these devices are used at different stages of their recovery could be an issue.

So, I think that the complex clinical presentation requires much more stringent research protocols to determine its effectiveness.

DR. HURST: Thank you.

Dr. Yang.

DR. YANG: So, for (a), I think yes, it does adequately define the target population.

For (b), it's not within my clinical expertise to comment on what the similarities and differences are.

For (c), no, I don't think there are any additional risks.

For (d), I think yes, that there is enough evidence to demonstrate that it's safe.

And (e), no, I don't think there's enough available scientific evidence.

DR. HURST: Thank you.

Dr. Good.

DR. GOOD: Well, first of all, does this statement adequately define a target population? I agree it's a little bit better than the rather non-specific terminology before, but I also agree with the comment that was made here that there may be some differences about the time that you're going to be treating them; is this during withdrawal, is this during -- you know, two months after they're abstinent? I mean, I think there are some questions about that.

The (b), I really can't comment on that either, about similarities and differences.

(c), is there increased risk? I don't think so.

(d), does the available scientific evidence adequately demonstrate the absence of unreasonable risk developments, injury? I think yes.

And then (e) is a sticking point, and I agree that the bar is even higher here since they would have had to fail other treatments. And as I recall, there are only seven or eight or nine studies or something like that that were presented in support of this particular indication. So, the answer is no, there is not enough evidence.

I will just editorialize by saying I'm very sympathetic to this. I think this is a very, very major problem, and it would be very, very valuable to have non-pharmacologic treatments that are effective. I am very sympathetic, but I just don't think there's enough evidence to demonstrate assurance of effectiveness.

DR. HURST: Thank you.

Dr. Dorsey.

DR. DORSEY: So, just one language thing. I would say the treatment of depression, anxiety, and insomnia in adult patients with a substance abuse disorder as opposed to substance abuse patients. So, for (a), I think yes.

For (b), I would defer it to colleagues of more expertise, who care for individuals with substance abuse disorders.

(c), no. I don't there are any significant additional risks in this population.

(d), yes.

And (e), no.

DR. HURST: Thank you.

My sense of the Panel is that -- sorry. Dr. Kotagal.

DR. KOTAGAL: Thank you.

With regard to (a), yes, it adequately defines a target population.

With regard to (b), I think the neurobiology of substance abuse may be different from that of depression and insomnia. Otherwise -- and so that's one issue, and I agree with Ms. Carras that their acceptance of a device versus drug may be different, so that's that.

And with regard to (c), are there any additional risks in this patient population that have been identified? No.

With regard to (d), there are no additional risks in this patient population, again.

(e), there is insufficient evidence for effectiveness.

DR. HURST: Thank you, Dr. Kotagal.

So, my sense is that with respect to adequate definition of a

target population, I think more felt that it probably did define a target population, particularly when we consider the off-label use that really, as was pointed out, has become standard in many instances, particularly with devices that are labeled for relatively narrow indications. Nevertheless, there was a considerable proportion of the Panel that felt that this did not adequately define a target population.

With respect to Number 2, generally, I think that the answer was yes, although there was a lot of us on the Panel who expressed somewhat a lack of experience in treating this population.

(c), no, pretty much across the board. There do not seem to be additional risks that should be considered for the substance abuse population.

(d), available scientific evidence adequately demonstrate the absence of unreasonable risk; that was yes pretty uniformly throughout the Panel.

And available scientific evidence demonstrate reasonable assurance of effectiveness. Pretty uniformly no among many of the members of the Panel. Three felt that there was a demonstration of reasonable assurance of effectiveness for that indication.

DR. EYDELMAN: Thank you very much.

MR. MARJENIN: And that concludes our questions for today.

And I'd just like to thank the Panel and thank all of the FDA

presenters and all of the petitioner presenters and all of the open public hearing presenters. I know that there has been a lot of work that went into all of the preparation and information that was presented today, so I'd just like to thank everybody.

DR. HURST: Thank you.

At this time, the Panel will hear summations, comments, or clarifications from the FDA. And we'd like you to limit that to three minutes, please.

DR. EYDELMAN: The only thing I wanted to add to Tim's summation is to thank my team for all the hard work that they put in, in preparation for today. That concludes FDA's remarks.

And thank you to all the Panel members for very, very thoughtful discussion. We really appreciated everybody's comments.

DR. HURST: Thank you.

Are there any summations, comments, or clarifications from the petitioner? Each of the petitioners has three minutes. Please approach the podium one at a time based on the order of your presentations.

MR. ELDER: Scott Elder again from Electromedical Products International, Inc.

I'd like to thank you all for taking the time to be here today and to hear their presentations.

I would like to point out that there's an inherent unfairness to

this procedure in that we received, just yesterday, the FDA's list of studies that were excluded from our presentation. And I believe if those studies were more accurately considered by this Panel, that you would conclude that there is valid scientific evidence establishing that the device is both safe and effective.

But, obviously, we did not have the time to respond to the deletions of studies for reasons which I would believe all of you would find invalid if we had time to discuss that. But when you have 45 minutes to present your device and all the science, some things are going to be left out, unfortunately. And when you have a day to prepare a response to their deletions of a lot of good research, you are going to, unfortunately, not have time to address it.

But, again, I thank you for your time because you were very thoughtful and very courteous and asked wonderful questions. Thank you.

DR. HURST: Thank you.

DR. XENAKIS: I'm Steve Xenakis.

I want to again also thank the Panel members and the FDA for their professionalism, conscientious approach to this problem.

Focus my remarks to a dilemma that we, as physicians, encounter that is represented and captured in this hearing today. And that is how we reconcile, respectively, our role as scientists and our role as humanists. And what, respectively, our responsibilities are to what is the

advancement of our disciplines and professions in the interest of our patients, and what our responsibility is to our patients who come to us, not only vulnerable but clearly suffering from the life circumstances that they have encountered.

And I have attempted today to illustrate to you that I believe that the overwhelming responsibility that we have to the welfare and quality of life of our patients far exceeds what is the confidence that we have in our scientific method. And I say that as a clinician who has soldiers and veterans and other patients come to me suffering with the problems of anxiety, depression, insomnia. And I say it as a general who sat and advised the most senior leaders in the Department of Defense and looked out to what would be the consequences of 10 years of war.

And having served during the Vietnam War and watched my colleagues and fellow soldiers who then went out for years and suffered with their PTSD that took our profession, allow to establish and validate, as a diagnosis -- it took our profession a while to recognize the effects of Agent Orange.

When we have groups of patients, less than 50% who are satisfied with the treatments that we are providing, do we not have a responsibility to take a reasonable risk when we acknowledge, as a group, that the risk for a particular treatment is infinitesimal? So, that denominator magnifies what the effect is of the numerator and what the benefit will be

from the treatment.

And I ask you, as fellow physicians and citizens, as Americans, to consider that. We don't have 2, 3, 5, or 10 years to wait for the clear scientific evidence and compelling evidence to come out and say yes, we're going to certify this treatment. We can do it in a smarter and more reasonable way now.

Thank you. I'm glad you can indulge me. I do feel passionate about this.

DR. HURST: Thank you.

DR. WORCHEL: Thank you for those wonderful comments. I want to echo those. Thank you to the Panel for your professionalism, your concern, and your diligence in going through these studies.

You know, our dictum is to do no harm, and I think you all very adequately determined that there is no harm associated with this treatment. There is obviously controversy as to the efficacy with regards to the clinical readers that are required by the FDA, but I do think speaking to the C.F.R., which was done here, the preponderance of evidence does support that there is an efficacy and given, as we just heard, once again, the denominator with regards to risk is zero.

What we're effectively doing, if we categorize this as a Category III device, is essentially denying our patients an opportunity for a treatment which may be effective when we have no other definitely effective

treatments that don't also carry a high risk of side effects, and in some patients, the treatments themselves made them worse, and that's what's written in the journals.

I would ask you to consider, and I think this was a valid concern, with regards to target populations, anxiety, insomnia, and depression, are they categorical, are they dimensional?

If we could perhaps consider language changes for this device that would allow it to be used with the language that would essentially indicate that, you know, for the treatment or for the amelioration of symptoms of anxiety, depression, and insomnia, this device may be effective. I think that's as good as it can get.

I think it addresses that we're not really dealing with specific DSM "whatever number it's going to be" diagnoses, but we're dealing with symptoms; we're dealing with absolutes. I mean, we don't give an NSAID with a particular effect saying it's only good for inflammation in. We say it's good for inflammation as a symptom in or aspirin for fever of.

So, I would ask you to consider so that we don't take away an option, which I think all of us in our hearts know is likely to be effective, although maybe not under these clinical rigors demonstrated to be effective. So, please consider changes in the controlling language that would allow us this option, which I think is so valuable to our patients. Thank you.

DR. HURST: Thank you.

(Off the record.)

(On the record.)

DR. HURST: So, we'll go ahead with, first of all, Dr. Alexandrov. Do you have any comments?

DR. ALEXANDROV: I think that, for the manufacturers of this device and I think that for the patients that have received care with this device, that there's a fantastic opportunity now that lays before you, and that is to really pull together and do some compelling research that supports the effectiveness and the safety of this device.

I think that while we've not found any compelling data that would tell us that it is highly unsafe, that the potential to move to a symptom-based paradigm away from a discrete diagnostic paradigm would open the door for the device manufacturer and for patients to potentially benefit from this if we have some well-designed trials that can show us that, indeed, this device can make a difference. And I think that's very important for consumers.

DR. HURST: Mr. Mueller, do you have any comments?

MR. MUELLER: Dave Mueller.

Yeah, I'd love to make a speech, but I think I'll just stay quiet this time. Although I did like the idea of changing the -- the FDA can work with the manufacturers to change the C.F.R. in order to make it feasible to go Class II.

DR. HURST: Ms. Carras, do you have any comments?

MS. CARRAS: I would just have to say that I am struck by the fact that FDA is considering putting this in the classification with life-threatening or life-sustaining devices, and I feel like, given what the Panel has said about its estimation of the risks associated with this device, that unless the FDA believes that there is no chance of any sort of benefit, that it wouldn't make sense to categorize it in Class III.

DR. HURST: Thank you.

I'd like to thank the Panel, the FDA, and the petitioners for their contributions to today's Panel meeting.

Dr. Eydelman, do you have any other final remarks or comments?

DR. EYDELMAN: Just to thank everybody once again for a very productive meeting.

DR. HURST: Thank you.

The February 10th, 2012 meeting of the Neurological Devices Panel is now adjourned.

(Whereupon, at 5:15 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

NEUROLOGICAL DEVICES PANEL

February 10, 2012

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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CATHY BELKA

Official Reporter